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FOREWORD

THIS first issue of *Circulation*, the official journal of the American Heart Association, represents a major step toward the realization of an ambition long cherished by the Editorial Board and by many of our members; namely, the creation of a scientific journal that shall be acknowledged as foremost in the world among those devoted to a special field of medicine. This step represents no mere change in name, format and publisher, but a revision also of content and purpose. The name *Circulation* was selected by the Editorial Board and the Publisher as that which most clearly indicates the journal's new scope—the entire circulation rather than the heart alone. We have advanced beyond the limitations of classical "cardiology" into the over-all study of the whole circulation.

The creation of the outstanding journal we desire will need the full understanding of these aims by all our subscribers and the active cooperation of hundreds of potential contributors. Most of those who read this foreword are already aware of the recent change in structure and purposes of the American Heart Association. From the original small organization of doctors interested in the purely scientific aspects of cardiovascular disease, it has grown into a large national voluntary health agency, with wide interests and broad responsibilities. In this change the scientific activities are safeguarded and continued at an even higher level under the guidance of the Association's Scientific Council. The Council has placed the immediate responsibility for the journal in the hands of a special Committee on Publications. This Committee will give all possible support to the Editorial Board and the Publisher for the purpose of reflecting in the journal the high standards which the Association has set. The Editorial Board itself has been enlarged to include representation of newer technics and additional specialties such as roentgenology, public health and preventive medicine, anticoagulants, and catheterization of the heart. It is intended that the membership of the Board will be so maintained that it is constantly and truly representative of all groups interested in the circulation, both clinical and investigative.

Circulation, then, is addressed to all those interested in the cardiovascular system in health and disease—the research scientist, the specialist, the practicing physician. Its intention is to include articles in the basic sciences relating to this field and papers representing the finest type of clinical research, as well as those which are mainly "practical" in their application. Recent years have witnessed a remarkable widening of interest in the physiologic and biochemical aspects of the circulation. The journal would fail in one of its most important functions if it did not encourage publication of articles in these and other basic fields. It is the firm purpose of the Editor, the Editorial Board and the Publisher to avoid making it on the one hand a journal so exalted in its aims that only a handful of scientists could read it intelligently and, on the other hand, a purely clinical journal which would have little interest for the investigators who are advancing the boundaries of our knowledge so rapidly. A program of such scope demands a finely balanced policy of selection; it is our belief that this can be accomplished. To keep abreast of advances in these various fields, it is planned to publish all papers within six months of their acceptance.

It is clearly impossible to create a journal that will please everyone; such a goal, however, may be kept in view. It is our intention to publish in *Circulation* papers, abstracts, reviews and special articles of such high calibre that they will receive the unqualified approval of those most competent to judge them. We earnestly request your frank criticisms and suggestions toward this end.

H. M. MARVIN, M.D., President,
American Heart Association

Blood Coagulation and the Practical Significance of Recent Advances in Knowledge of Prothrombin and Ac-Globulin

By WALTER H. SEEGERS, PH.D.

An attempt is made to describe the nature of the chemical interactions participating in blood clotting. In the laboratory, thrombin can be derived directly from prothrombin without the physiologic activators calcium, thromboplastin, Ac-globulin, and platelet derivatives. The newly recognized clotting factor, Ac-globulin, is essential for normal physiologic hemostasis. Plasma Ac-globulin concentration decreases in experimental liver damage, temporarily with dicumarol administration and may increase from high doses of aminophylline. In citrated storage plasma it is stable for a week but not in oxalated human plasma. Compared with other species, human plasma contains a low concentration of Ac-globulin. Methods for Ac-globulin analysis have been developed; perhaps more important is the fact that the two-stage method for prothrombin analysis need no longer be considered a complicated procedure.

IT IS a simple matter to arouse curiosity concerning the problem of blood coagulation. If one begins a conversation with someone who has had only limited experience in biology or for that matter with any scientific subject, it may be suggested that blood will clot a few minutes after it is shed, and that this must be something very special, because that same blood remained fluid as long as it was contained in the vessels. It is at once evident that this clotting mechanism is a powerful defense against fatal hemorrhage. Furthermore, it is logical that the problem of thrombosis is largely a matter involving the clotting of blood within the vessels themselves. It is more difficult to convey the idea that the problem of blood coagulation encompasses fundamental problems in biology. This broader aspect even now escapes the attention of most scientists. We are dealing with the interactions of marked molecules. Each one of them is marked as distinctively with respect to the other as if it contained a radioactive tracer element. Just as the radioactive materials can be traced through complex metabolic phenomena so the marked protein molecules can be traced through many complex interactions in the metabolic machinery and in the test tube. By understanding the nature of protein reactions, we get closer and closer to understanding the nature of living processes. And we can think of the complex act of blood coagulation as being an operation of life.

I would like to be as practical as possible in this discussion. First, an attempt will be made to describe in the simplest manner possible the nature of the chemical interactions which participate in blood clotting. This is appropriate because a clear concept cannot be obtained from the literature. Second, a new clotting factor, accelerator globulin, has been recognized. In order to understand the relationship of this factor to prothrombin it is of prime importance to know certain basic facts about prothrombin itself. For that reason some of the new information on prothrombin will be described. Third, important information on Ac-globulin is already available and the following topics can be discussed briefly: (a) Ac-globulin changes in storage plasma, (b) effect of experimental liver damage, (c) Ac-globulin concentration in human plasma as compared with other species, (d) changes produced by aminophylline, and (e) the effect of dicumarol administration.

Figure 1 symbolizes my first assignment; namely, to present rapidly our current knowledge of the fundamental nature of blood coagulation. It requires a brief summarization of the main information in approximately 10,000 pa-

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pers. In a large proportion of these papers the conclusions are pushed beyond the just limits of the data. The result is great confusion, and, for want of principles to direct his choice, even the critical reader can adopt mistaken viewpoints. Eventually the true pattern must become clear and it seems likely that the main paths are already well outlined.

It is advantageous to consider the blood clotting mechanism as though two mechanisms had been provided: one involving the interaction of the proteins which are concerned with clot formation; and, second, a mechanism provided for the removal of a clot. The latter mechanism is not primarily an inhibitor of clot formation but can be regarded as a separate system. On the basis of that general viewpoint the schematic presentation of the clotting mechanism of figure 1 was arranged.

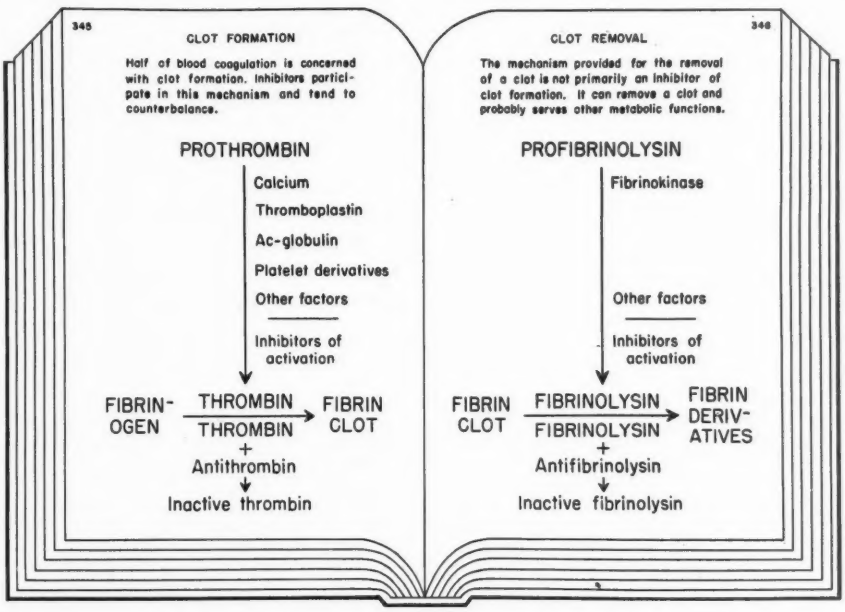

FIG. 1.—A diagrammatic representation of blood clotting

Prothrombin is constantly present in the blood, provided there is an adequate amount of vitamin K available for its synthesis by the liver. Thrombin is derived from the prothrombin and it is the substance which reacts with the fibrinogen of the plasma to form fibrin, which is the clot.

From purification work we know that prothrombin is a glycoprotein. Its normal concentration is about 15 to 20 mg. per 100 cc. of plasma. This means that the average individual on dicumarol therapy manages to get along with approximately 20 mg. of prothrombin. Purified material has powerful clotting activity when fully activated. In fact, a milligram is almost sufficient to clot 2.0 liters of standardized fibrinogen solution in fifteen seconds.

In the clotting of fibrinogen by thrombin, calcium tends to have a favorable influence but is not essential. A variety of artificial substances from the laboratory, such as acacia, gelatin and some other colloids, also make it much easier for thrombin to clot fibrinogen. Material of platelet origin also aids in that respect. All of these substances which are not essential for the action of thrombin but have a favorable influence on thrombic activity have been referred to as fibrinoplastic agents.

There are a number of substances which participate in the activation of prothrombin. For the physiologic activation of prothrombin, calcium is essential and must be present in optimum concentration. Thromboplastin is also

needed and although potent concentrates of thromboplastin can be derived from almost any tissue the exact chemical nature of the reactive groups in thromboplastin is still not known. Lately there has been some interest in thromboplastin as related to toxemia of pregnancy. There is evidence to indicate that it gets into the maternal blood circulation and is in part responsible for toxemia of pregnancy. Actual proof is lacking but the possibility is so real that the problem is being studied thoroughly.

Accelerator globulin is a plasma protein which is essential for the rapid activation of prothrombin. A deficiency of this globulin may result in a bleeding tendency. Dr. Owren, in Norway, described the deficiency of his patient, a 29 year old woman. At the age of 3½ years she had a severe nose bleed which stopped spontaneously in a few hours. During adolescence she had frequent nosebleeds. There was difficulty with bleeding during menstruation. At the age of 29 years the clotting time by capillary method was fifteen minutes, and in test tubes twenty-five minutes. Clot retraction was normal. The prothrombin time was seventy to eighty seconds. Vitamin K was of no value, and it could be shown that this patient was not deficient in prothrombin. More will be said about accelerator globulin later.

The platelets furnish material which participates in the activation of prothrombin but contrary to the view held for many years they very likely do not furnish very much thromboplastin activity. The activity which they supply is more nearly like that supplied by Ac-globulin. In other words, it is material which acts in conjunction with thromboplastin.

It has been indicated in figure 1 that there are other factors which participate in the activation of prothrombin. Some of these are as yet not well characterized. It is known that the deficiency in hemophilia is due to a lack of essential material required for the activation of prothrombin. Probably the hemophiliac lacks a plasma factor which acts in conjunction with platelets to furnish the equivalent of thromboplastin activity.

Calcium, thromboplastin, Ac-globulin, platelet derivatives and other factors all contribute to the activation of prothrombin, and under appropriate conditions they are capable of being prevented from doing so by a number of inhibitors of prothrombin activation. The best known inhibitor is heparin. From experiments involving total body irradiation it seems probable that substances quite similar to heparin may also exist. Another inhibitor has recently been recognized and is referred to by the term "antithromboplastin." Whether it acts specifically against thromboplastin remains to be proved. All that is known is that it inhibits the first phase activation process. Purification work done in two different laboratories shows that this inhibitor may be a specific kind of lipid. Dr. Tocantins in Philadelphia and Dr. Overman and Dr. Wright in New York have independently obtained materials possessing interesting physiologic properties, and Dr. Tocantins believes that this inhibitor is one of the important factors in hemophilia. It seems likely that this substance may be a useful anticoagulant.

It has long been known that plasma will inactivate thrombin. This is the antithrombic activity of plasma. Our recent studies of the problem indicate that there is only one antithrombin and that its activity is not influenced by heparin. It is capable of destroying large quantities of thrombin. An effect which has probably been mistaken for antithrombic activity of plasma can be ascribed to an odd phenomenon which has to do with adsorption. For example, when thrombin clots fibrinogen, much of the thrombin is physically adsorbed on the clot. The amount of thrombin adsorbed is proportional to the concentration of the thrombin used for producing the clot. Furthermore, the amount adsorbed will be increased if heparin and crystalline albumin are in the reaction mixture. Heparin alone or crystalline albumin alone are not sufficient. The two must be present simultaneously. The supposed antithrombin effect of heparin is concerned with thrombin adsorption and interference with the thrombin-fibrinogen reaction. It is not properly regarded as an antithrombin effect because the adsorbed thrombin can be recovered by dissolving the clot with fibrinolysin.

There is also a mechanism which is concerned with the lysis of a clot and this mechanism

bears a striking resemblance to the clotting system. A plasma substance called profibrinolysin becomes activated to fibrinolysin and this enzyme can dissolve a fibrin clot.

Like prothrombin this profibrinolysin must first be activated and an activator has been discovered in many tissues and is referred to by the term "fibrinokinase." So far it has not been possible to make potent preparations of this activator, but artificial substances have been employed. For example, profibrinolysin is activated by shaking with chloroform. It can also be activated by an enzyme found in certain bacteria. For example, staphylokinase or streptokinase are potent activators. When bacteria cause fibrin to lyse it is thought to be the result of their capacity to activate plasma profibrinolysin.

Presumably there are also inhibitors of profibrinolysin but so far none have been described in the literature.

Fibrinolysin can be inactivated by plasma antifibrinolysin. This antifibrinolysin of plasma is a powerful inhibitor found in the plasma of almost all species. Antifibrinolysin concentration in plasma is considerably increased in folic acid deficiency. It is also increased in concentration in a variety of pathologic states; for example, pernicious anemia, cirrhosis of the liver, coronary thrombosis, pneumonia, and intestinal obstruction.

A review of the two summaries in figure 1 shows that the two systems bear a striking resemblance to each other. This outline may constitute oversimplification, but it has the advantage of being easy to comprehend and is easily remembered. Further details can be developed as subtopics of these main fundamentals.

It can be seen that prothrombin occupies a central and dominant position in the clotting mechanism. It is indicated on the outline of figure 1 that thrombin can be derived directly from prothrombin; and that calcium, thromboplastin, Ac-globulin, platelet derivatives and other factors are accessory factors. The inhibitors are also accessory factors and may counterbalance or overpower the activators.

How do we know that this view is correct? It is generally conceded that the answer to such a question can be supplied only by working with purified clotting factors. There are altogether too many variables when all of them are present and acting simultaneously, and being measured by only one indicator; namely, the rate of clot formation.

There are two main philosophies or approaches to the problem of plasma fractionation. One maintains that plasma should be fractionated systematically into its several components and when more and more subfractions are made we will eventually obtain all of the plasma entities in purified form and in substantial yield. There are several fallacies in this philosophy which make it untenable at times. For example, many prothrombin fractions have been described. Some were products of systematic fractionation procedures, but the yield and degree of purification was unsatisfactory. The difficulty arises in that a reagent which may not be damaging to albumin or some other component may be very damaging to prothrombin. Another consideration which has a bearing on the problem is the relative concentration of the several proteins. The concentration of albumin in the blood is roughly 2 per cent whereas the concentration of prothrombin is less than 0.01 per cent. The concentration of prothrombin is thus a special purification problem.

The single objective route is the other approach to the problem of plasma fractionation. One centers all attention on one of the plasma constituents and plans all kinds of fractionation procedures with the aim of getting that component in good yield and purity. It gives plenty of opportunity for trial-and-error probing. This approach may be regarded as the poor man's approach and is the more common way in which plasma proteins are obtained for scientific study. In this way we have been able to obtain prothrombin in good yield and a reasonable degree of purity, but only after ten years of work. That may be stated in another way. About 1,800 fractionation procedures were tried before satisfactory products were obtained.

It has been possible to do a number of experiments with the purified material. One is of special importance. When the purified prothrombin is dissolved in a 30 per cent solution

of sodium citrate it becomes activated to thrombin. It is essential that sodium citrate be in high concentration although some activation takes place in 5, 10, and 15 per cent solutions.

The curve in figure 2 represents the thrombin activity found when purified prothrombin was activated with 30 per cent sodium citrate solution. Thrombin began to appear at the end of three hours. At the end of five hours the concentration began to increase rapidly. This rapid increase continued through the next four hours. Thereafter thrombin production was slow again. The curve, as drawn, represents the mathematical curve for autocatalysis and it can be seen that the experimental points fall reasonably well on the curve. There are

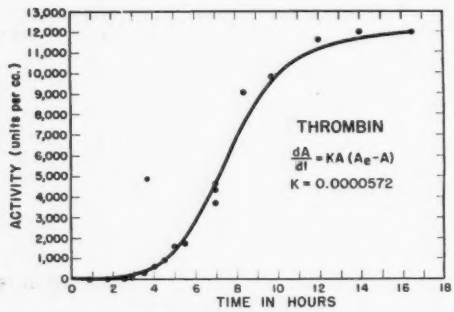

FIG. 2.—Activation of purified bovine prothrombin by dissolving 12,000 units of prothrombin in 1 cc. of 30 per cent sodium citrate solution. The curve shows the thrombin concentration which developed in the solution.

many references in the literature to autocatalytic formation of thrombin but I believe this is the first unequivocal demonstration of such a phenomenon. To obtain additional evidence of autocatalysis, thrombin was added to the prothrombin solution at various times during and before activation had begun. Such additions of thrombin always caused thrombin to form more rapidly.

Now we can go back for a brief review. It was indicated that prothrombin occupies a dominant position in the clotting mechanism. The outline of the clotting mechanism indicates that thrombin can be derived directly from prothrombin, and that calcium, thromboplastin, Ac-globulin, platelet derivatives, and other factors are catalysts of prothrombin activation. It was asked, how do we know that this is correct? The answer has been supplied. Prothrombin has been isolated. Evidence for purity has been obtained. The prothrombin was activated autocatalytically in concentrated sodium citrate solution, thus showing that prothrombin itself contains all the structural material needed for thrombin and nothing needs to be added by the activators of prothrombin.

In figure 2 it can be seen that it took about sixteen hours for the activation of the prothrombin. Obviously this is far too slow to be of any value for avoiding a fatal hemorrhage. What is required for rapid activation of prothrombin? It has been shown that calcium and thromboplastin are not sufficient. Another substance is essential; namely, plasma accelerator globulin. It functions as a co-factor of thromboplastin, so that calcium, thromboplastin, and Ac-globulin together will activate purified prothrombin rapidly.

Ac-globulin is a normal plasma constituent and has already been obtained in concentrated form. It is less soluble in ammonium sulfate solution than prothrombin. It is more sensitive to acids and alkali than prothrombin. It is not adsorbed on barium carbonate whereas prothrombin is. Like prothrombin it is found in plasma in trace quantities.

Its exact position in the clotting mechanism has not been established as securely as it eventually must be. A number of sound experiments and lines of evidence indicate that the following diagram may represent how Ac-globulin participates in prothrombin activation.

$$\text{Prothrombin} + \text{Thromboplastin} \xrightarrow[\text{Platelet accelerator}]{Ca^{++}} \text{Thrombin}$$

$$\text{Plasma Ac-globulin} \xrightarrow{\text{Thrombin}} \text{Serum Ac-globulin}$$

$$\text{Prothrombin} + \text{Thromboplastin} \xrightarrow[\text{Platelet accelerator}\ \text{Serum Ac-globulin}]{Ca^{++}} \text{Thrombin}$$

$$\text{Fibrinogen} \xrightarrow{\text{Thrombin}} \text{Fibrin}$$

First, a small amount of prothrombin is activated by calcium, platelet accelerator, and thromboplastin. The small amount of thrombin formed can then activate plasma accelerator globulin. Then the interaction of prothrombin, thromboplastin, calcium, platelet accelerator, and active accelerator globulin is rapid. Throm-

lin is thus formed rapidly after a slow beginning.

Quantitative methods have been developed for measuring its activity in plasma. We believe that these methods are reliable and give a reliable measure of Ac-globulin activity. These methods have been applied to the following studies: (a) Ac-globulin concentration in storage plasma. (b) Ac-globulin concentration in experimental liver damage, (c) Ac-globulin concentration in the plasma of various species, (d) Ac-globulin concentration during aminophylline administration, and (e) Ac-globulin concentration during dicumarol therapy. Simultaneously, the prothrombin concentration was measured and it was possible to get an indication of the variation of both of these plasma constituents in the same experiment. The finding in these experiments will be reviewed briefly.

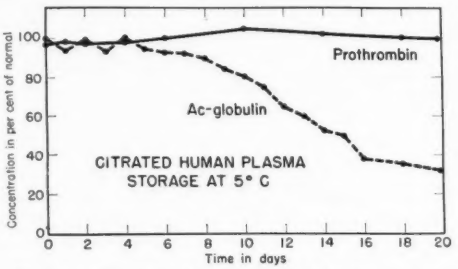

FIG. 3.—Prothrombin and Ac-globulin activity in citrated human plasma stored at a temperature of 5 C.

In stored citrated human plasma the prothrombin concentration remains normal for long periods of time (fig. 3). A number of years ago there was much discussion about the disappearance of prothrombin in stored plasma. At that time we were shipping plasma by surface carrier and using the plasma for the industrial production of thrombin for use as an hemostatic agent. According to the literature of that period we should never have been able to obtain any thrombin from such plasma.

Ac-globulin is also stable for a period of about a week, but thereafter its activity begins to disappear fairly rapidly. It is an interesting fact that Ac-globulin is not stable in oxalated human plasma. As a simple guide to the physician it is satisfactory to rely on storage plasma as a source of Ac-globulin if the plasma is not unduly old. There are many interesting problems regarding Ac-globulin stability which, however, have a primary bearing on research work.

In experimental liver damage both the prothrombin concentration and Ac-globulin concentration drop. In this experiment with dogs given deep chloroform anesthesia, the activity of both plasma factors decreased. The Ac-globulin recovery was perhaps a bit more rapid than that of the prothrombin. We do not know that an acute experiment of this kind on animals can be taken as any indication as to what would happen in chronic diseases in man, but presumably one could expect a drop in Ac-globulin concentration. We believe Ac-globulin and Owren's Factor V to be one and the same substance, and Dr. Owren has reported that Factor V concentration decreases with liver damage in the human being. Accordingly, we are, therefore, amplifying and extending his work.

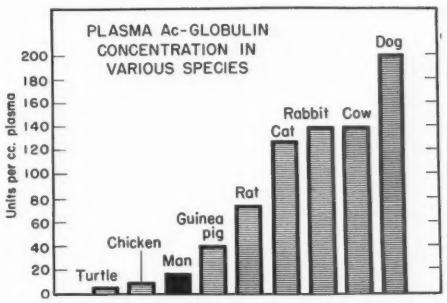

FIG. 4.—Relative plasma Ac-globulin concentration in various animals.

It is always an interesting matter to know where man stands in relation to other species, and the summary in figure 4 shows that he has an unusually low Ac-globulin concentration. For example, the guinea pig, the rat, the cow, the rabbit, and the dog all have far more of this accelerator factor than man. Only the chicken and the turtle have less and even they show up relatively well. No one knows what this may mean. Man has a large quota of prothrombin just as does the dog, the cow, the rabbit and the cat, and if Ac-globulin is necessary for the rapid activation of prothrombin it makes one wonder whether a slight decrease

in Ac-globulin might not be of considerable consequence. The difficulty, of course, resides in the fact that the significance of the prothrombin/Ac-globulin ratio is not understood as yet.

Some time ago it was reported by Link and his associates that the methyl xanthines, including aminophylline, can alter the extent and duration of hypoprothrombinemia caused by dicumarol. It was their view that the methyl xanthines, including aminophylline, are capable of producing a hyperprothrombinemia. Their original work became involved in contradictions. Being in the possession of a method which would measure both prothrombin concentration and Ac-globulin concentration quantitatively, we were prompted to do some experiments with aminophylline. In the experimental result shown by figure 5 it is seen that aminophylline administered in the amount of 100 mg. per kilogram of body weight in the dog caused a very prompt increase in Ac-globulin concentration. There was also a temporary increase in prothrombin concentration. Later this tended to drop somewhat below normal and definitely returned to normal in thirty days. The high Ac-globulin concentration persisted for awhile and then declined to normal over a period of about thirty days. This experiment has been repeated in several animals with the same results. One thing which was most impressive about these experiments was the high dose required to obtain the response. This work was done on animals and further information is needed on the effect which may be produced in human beings. Preliminary indications come from the work of Dr. John Olwin of Chicago who has commonly found it to be the case that far more dicumarol is required when aminophylline is also given. His work shows this to be true in about one-half of the human patients on which he has data.

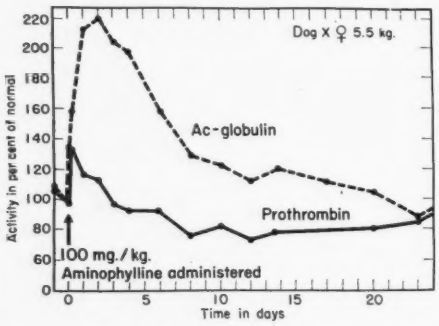

FIG. 5.—Change in plasma Ac-globulin and prothrombin concentration in the dog after giving a single dose of aminophylline.

The administration of dicumarol may also effect the plasma Ac-globulin concentration. In experiments performed with dogs, prothrombin concentration decreased in a manner typical of many experiments recorded in the literature. The Ac-globulin concentration also decreased, but only slightly. When the prothrombin began to reappear in the plasma the Ac-globulin concentration not only returned to normal levels but in addition it increased above normal for a period of time.

There was also opportunity to study human patients on dicumarol therapy. This was in cooperation with Dr. John Olwin of Chicago. As in the experiments on dogs, it was found that Ac-globulin may decrease when the drug is first given. When the maintenance dose is being administered this does not further depress the Ac-globulin concentration. On the contrary, the Ac-globulin concentration returns to normal while the prothrombin is being maintained at the desired low levels.

Ac-globulin concentration may quite definitely be an important factor in dicumarol therapy. There is an interesting theoretic speculation in regard to the safety of the drug. If Ac-globulin concentration does not decrease appreciably but the prothrombin concentration drops to a low level, the Ac-globulin may compensate for a low prothrombin level. This implies that when the physician progressively lowers the prothrombin by administering dicumarol the Ac-globulin becomes a safety factor which acts as a buffer, causing the remaining prothrombin to be utilized very efficiently. That may be premature speculation; but it is logical, and, I hope, a comforting thought.

It must be evident that methods which are capable of giving reliable quantitative values for prothrombin concentration and reliable values for plasma Ac-globulin concentration are practically essential in the research labora-

tory, and perhaps no one would dispute their desirability for general use. At the present time it must be admitted that the analysis for Ac-globulin activity which was used in the experiments just described is somewhat cumbersome.

What is the status with respect to prothrombin analysis? The two-stage procedure for prothrombin has long had the reputation of being impractical for general use. Often reviews will contain a statement such as the following: "Practically all investigators agree that the two-stage is much more laborious than the one-stage procedure. This precludes its routine use in most clinical laboratories." Such statements are becoming obsolete. First, the two-stage procedure for prothrombin analysis is a quantitative analysis for prothrombin whereas the one-stage procedure is not. It measures a variety of factors. Second, an effort has been made to simplify the two-stage method and to make the required reagents generally available. There has been considerable success in that connection. A detailed description of the two-stage method, recently published (Am. J. Clin. Path. **19:** 41, 1949), gives sufficient information for anyone to master the technic. Furthermore, the necessary reagents are being made available commercially. As a consequence, the clinical laboratory has at its disposal a very excellent method for measuring quantitatively the prothrombin concentration of plasma.

Summary

The main points of this discussion can be reviewed briefly. It is advantageous to consider blood clotting as though two mechanisms had been provided, one for clot formation and one for clot removal. Prothrombin is the substance which must be activated to form thrombin. There are many activators of prothrombin and their action may be counterbalanced by inhibitors. One of the activators is Ac-globulin, which is a plasma protein. It acts as a co-factor of thromboplastin and calcium. This newly recognized clotting factor must be considered in methods for prothrombin analysis. Relative to other species, man possesses a low concentration of Ac-globulin. It decreases in experimental liver damage, also temporarily in dicumarol therapy, and slowly in citrated human plasma after ten days of storage. With large doses of aminophylline the plasma concentrations may double.

Physicians are constantly expected to prognosticate. In contrast, this is not required of those who work in the laboratory. We are supposed to describe our experiments and be careful not to push conclusions beyond the just limits of the data. Now and then it is permissible to extrapolate. On that ground I am departing from data, but only for a moment.

Rapid progress has been made in our theoretical knowledge of the blood-clotting mechanism. Progress has been made in the control of hemorrhage, and in the control and prevention of thrombosis. There must be further endeavor not only to add to this knowledge but also to apply it effectively. One person has the following to say, "The truth is that fruitful progress occurs only when a large number of people are thinking together about the same sort of thing."

It is my understanding that this is the first time someone who is not himself a physician has presented the George Brown Memorial Lecture. I am very grateful for that, and if it was a bit abstract in spots, won't you please recall this sentence: Fruitful progress occurs only when all sorts of people are thinking together about the same sort of thing.

The Experimental Production of Intercoronary Arterial Anastomoses and their Functional Significance

By Herrman L. Blumgart, M.D., Paul M. Zoll, M.D., A. Stone Freedberg, M.D., and D. Rourke Gilligan, A.M.

Animal experiments were done to learn the degree of coronary narrowing required to produce the larger intercoronary collateral channels, their speed of development, and the degree of protection afforded the myocardium. Twelve or more days of 75 per cent narrowing were required to produce sufficiently rich anastomotic communications to protect the myocardium from damage, and to permit survival after superimposed acute complete occlusion. The physiologic and pathologic significance of the intercoronary collateral communications and the clinical implications in coronary artery disease are discussed.

THE CLINICAL manifestations of acute myocardial infarction are no longer regarded to be solely the result of an acute occlusion of a coronary artery. In some instances, acute myocardial infarction occurs in the absence of fresh narrowing or occlusion[1–5] while in other hearts the effects of acute occlusion may be partly neutralized by the presence of collateral circulation consequent to previous narrowing. Thus, acute myocardial infarction is to be regarded rather the resultant of two opposing processes; namely, the obstruction to blood flow by occlusive processes, and the compensatory development of collateral circulation which serves to offset the dire effects of coronary narrowing and occlusion.

Despite excellent studies of the collateral coronary circulation, the speed with which interarterial connections develop and the degree to which they protect the myocardium are imperfectly understood. Clinical and pathologic data on hearts with old coronary occlusion and with collateral circulation do not yield decisive answers. On examining such a human heart post mortem, only the net end result of the obstructive process and the compensatory bypasses is witnessed; one cannot determine accurately, even by microscopic study, how long previously the narrowing or complete occlusion occurred or when the collateral circulation developed.

To elucidate these problems, which are so important in the clinical management of coronary disease, recourse to animal experimentation was necessary. The experimental investigation reported below was designed to discover (1) whether acute narrowing of a coronary artery in an otherwise normal heart leads to the development of a collateral circulation; (2) the length of time necessary to establish such a collateral circulation; (3) whether the coronary collateral circulation developed after such a sudden narrowing is functionally effective in protecting the myocardium from the effects of a superimposed acute occlusion.

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Methods and Technic

Choice of Animal: A word of caution should be expressed regarding studies on the hearts of dogs. To be certain that any collateral circulation observed post mortem is due to the experimental procedure, one must be confident that such collateral pathways are not present normally in the heart of the experimental animal. In our original experiments undertaken on the dog with the Schlesinger technic[6] of injection plus dissection of the coronary arteries, the hearts of dogs often showed relatively large interarterial connections normally. In many experiments we could not conclude that the collateral vessels observed post mortem had been produced by us. Similar connections between the right, anterior descending, and left circumflex coronary arteries in the unoperated heart of the dog have been observed by Pianetto,[7] using the same technic of injection with colored lead-agar mass.

Some preliminary injections of normal pig hearts showed no interarterial coronary communications. In subsequent injections of 44 normal pig hearts (table 1, *A*), only one showed interarterial coronary

communications. They consisted of very fine, faintly visible twigs connecting the left anterior descending and right coronary arteries on the surface near the apex and were not large enough for transfer of color of the injection mass from one arterial territory to another. It should be noted that the communications established following narrowing of the coronary arteries are profuse, different in location, and of an entirely different magnitude, permitting a definite mixing of colored mass among the arteries over many parts of the heart.

Experimental Technic: Young pigs weighing from 5.6 to 20.0 kilograms received 0.5 mg. atropine sulfate preoperatively. Intratracheal ether anesthesia was employed.

The heart was exposed through an intercostal incision. The pericardium was opened; one of the major coronary arteries, the left anterior descending, left circumflex, or right, was carefully dissected from its bed and a ligature passed under it. A wire of known diameter was placed alongside the vessel and the ligature was tied snugly around both the wire probe and the artery. The probe then was withdrawn quickly; the duration of complete occlusion in this procedure was fifteen to forty seconds. Many control experiments showed that the temporary complete occlusion of the artery was not a factor in the production of collateral circulation. Prior studies have shown that brief complete occlusion does not cause cardiac lesions.[8]

The lumen of the artery within the tie was narrowed thereby approximately to the size of the wire probe. The wires utilized were 0.4 mm. to 1.2 mm. in diameter. The degree of narrowing produced by a wire of given size shows some variations. If the ligature is tied too tightly, the intima of the opposing sides of the vessel may become adherent or damaged and the vessel may remain occluded even after withdrawal of the wire. It is important to assure the re-establishment of patency of the lumen by gently prodding the artery with the finger and observing the flow of blood through it. In some animals, the failure of the artery to open after withdrawing the wire is probably due to the spasm of the artery induced by mechanical stimulation. Undue traction on the ligature, however, as it is tied around the wire and the artery may injure the intima and lead to progressive narrowing and final occlusion (Animals 41 and 42, table 3, *C*). In Animal 42, a thrombus had formed. If the ligature is drawn too loosely, the resulting lumen of the artery will be unduly large. This variation, however, has been reduced by experience. In any event, the degree of narrowing that has been produced can be measured with considerable accuracy post mortem. Subsequently the same artery was narrowed even more, occluded completely, or the animal was sacrificed without reoperation.

The coronary arteries were examined post mortem according to the injection plus dissection technic. In addition to cannulation of the left descending and the right main coronary arteries, the left circumflex artery was cannulated by transecting the artery just distal to its origin from the main left coronary artery. The usual lead-agar mass was used —colored blue for the left descending, red for the right coronary, and yellow for the left circumflex coronary arteries. In order to fill more completely any interarterial communications the technic of injection was slightly modified by application of negative pressure to one cannula and positive pressure to the other two in rotation. Final application of positive pressure of 180 mm. of mercury was made to the three cannulae simultaneously. In the hearts of normal pigs, the injection mass introduced in this manner into each of the three major coronary arteries remained within the confines of that arterial tree (fig. 1, *A*).

TABLE 1.—*Interarterial Anastomoses by Injection Method[6] in Control Pig Hearts*

	Total Number	Anastomoses		Remarks
		Number	Degrees*	
A. Normal pig hearts	44	1	+	
B. Operative controls without coronary narrowing or occlusion	11	1	+	Collagen values for left ventricle range from 0.38 to 0.57 grams % (average 0.49)

* Graded on scale of + to +++.

The lumen of the artery was measured by calibrated probes at the narrowed area and also at adjacent normal segments. The percentage reduction of the original cross-sectional area of the coronary artery was then calculated. Multiple, tagged, representative sections from various portions of the heart were studied microscopically. The amount of fibrosis was also determined by chemical measurement of the collagen content of specimens of the myocardium.[9]

RESULTS

Normal Control Group: In 43 of 44 normal pig hearts (table 1, *A*) no intercoronary anastomotic connections were visible. In one ani-

mal, fine intercommunicating twigs were seen between the left anterior descending and right coronary arteries on the surface of the heart over the apex.

Experiments in which no Intercoronary Anastomotic Connections Were Produced

Control Experiments of the Surgical Procedure: As in all experimental work, the possibility arose of having produced collateral circulation by adventitious factors in the operative procedure itself. In eleven experiments (table 1, *B*) exactly the same operative technic was practiced. These animals were killed after various stages of the operative procedure were performed; included in this group are animals killed during the operation and up to seven days thereafter. In 10 hearts no intercoronary anastomoses were visible. In one animal fine intercommunicating twigs were seen among the branches of the left anterior descending corot nary artery. No communications with the right or left circumflex arteries were observed. In 4 instances the collagen content of the left ventricle was determined; the values were 0.38 to 0.57 grams per cent of the net weight of tissue.

Control Experiments with Slight Narrowing: In three experiments, only very slight narrowing was produced intentionally to learn whether such relatively slight reduction in the lumen was sufficient to produce visible intercoronary connections (table 2, *A*). No anastomotic vessels were discernible on injection and dissection. The collagen values were in the normal range.

Experiments in which Coronary Narrowing or Occlusion Caused Cardiac Death: In 18 animals, cardiac death occurred within the first day after marked narrowing or complete occlusion of one of the major coronary arteries (table 2, *B*). In all instances, evidence of disturbed cardiac function was immediately obvious in the form of arrhythmias or cardiac dilatation. Ventricular fibrillation or cardiac standstill was observed within three to twenty minutes in 14 of the 18. In the other four experiments the chest was closed and the heart was not visible but, post mortem, the territory of the occluded artery exhibited the discoloration indicative of early infarction and edema or necrosis of the muscle. In 17 hearts no intercoronary anastomotic connections were visible (fig. 1 *B*). In Animal 5, fine intercommunicating twigs among the branches of the anterior descending artery were visible over the apex of the heart. In this experiment, the onset of ventricular fibrillation within three minutes after marked narrowing testifies to the functional inadequacy of these communications which are rarely seen in the normal pig heart. In all but 2 (Animals 24 and 29) of these 18 animals the coronary artery had been suddenly narrowed to less than 13 per cent of its original cross-sectional area. It may be concluded, therefore, that sudden narrowing to less than 13 per cent of the original area of the left anterior descending or right coronary arteries is generally incompatible with survival. The collagen values were normal in 5 or 6 instances, and on microscopic examination there was no myocardial fibrosis.

Experiments with Narrowing in which Animals Died of Noncardiac Causes: In 8 animals which died of noncardiac causes the interarterial coronary communications were absent (table 2, *C*). In the 2 animals (Animals 12 and 40), which had survived seven to fourteen days with a reduction to 8 to 21 per cent of the original cross-sectional area, intercoronary communications which one might have anticipated

FIG. 1, *A*.—(Pig No. 4.) Normal pig heart. Blue mass injected into left anterior descending, yellow mass injected into left circumflex, and red mass injected into right coronary artery. Each injection mass is confined to a single arterial tree. There is no intermixing of color.

FIG. 1, *B*.—(Pig No. 35.) Acute occlusion of mid-zone of right coronary artery was followed by death in three hours. Peripheral portion of right coronary artery was uninjected; no interarterial anastomoses. Early infarction of right ventricular myocardium.

FIG. 1, *C*.—(Pig No. 32.) Mid-zone of right coronary artery was narrowed twenty-five days before sacrifice; superimposed complete occlusion one day before sacrifice without subsequent infarction. Peripheral portion of right coronary filled with injection mass from left descending and left circumflex arteries by extensive anastomoses.

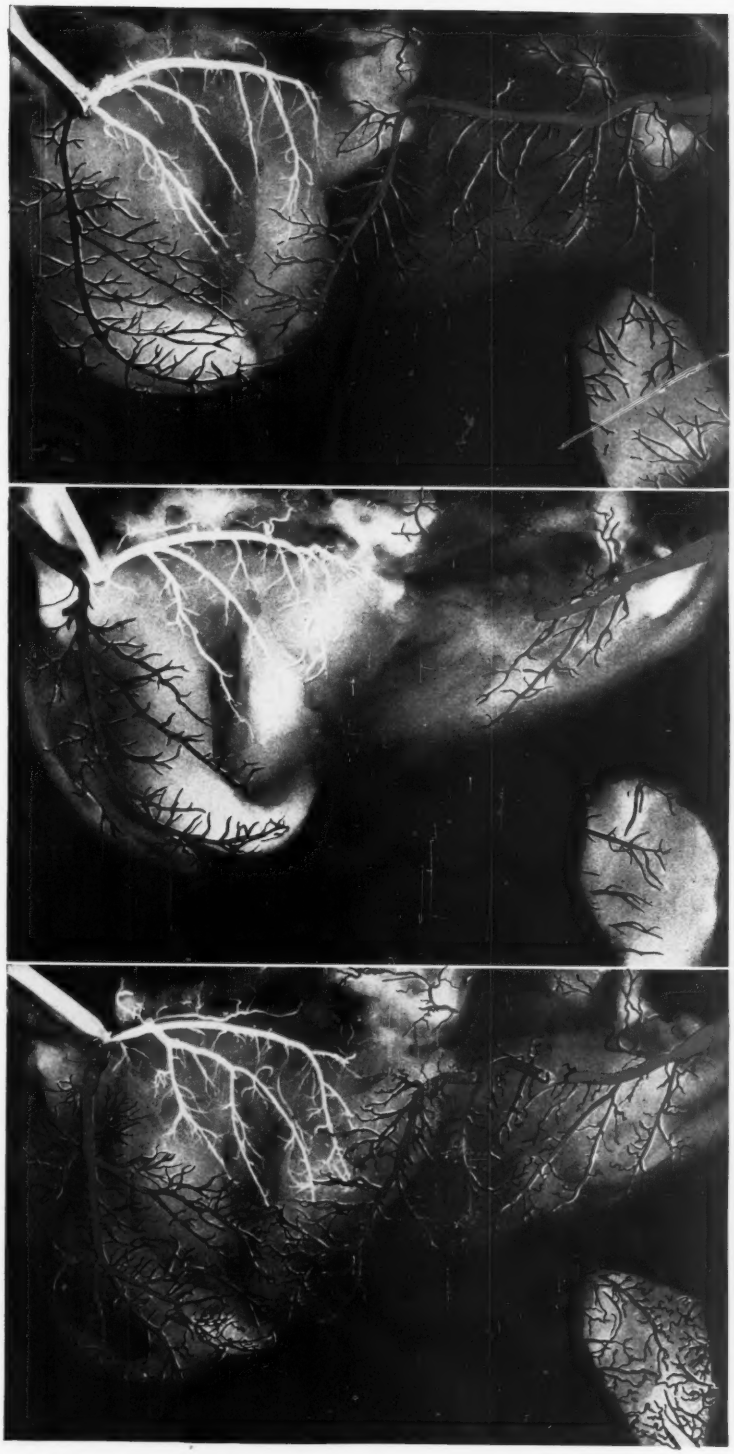

FIG. 1

TABLE 2.—*Experiments in Which No Intercoronary Anastomotic Connections Were Produced*

Animal Number	Artery Constricted	Size Lumen after Ligation (% Original Area)	Time before Death	Collagen (Grams %)	Remarks
			A. Experiments in which Slight Narrowing Was Induced		
48	RC	77	21 d	0.45	Sacrificed
49	RC	72	21 d	0.51	Sacrificed
51	RC	56	21 d	0.49	Sacrificed
			B. Experiments in which Narrowing or Occlusion Caused Cardiac Death		
5	LAD	—	5 h	—	Second marked narrowing was followed immediately by ventricular fibrillation and death. Fine surface anastomotic twigs between branches of LAD (graded +)
	LAD		3 m		
9	LAD	16	22½ h	—	Death from ventricular fibrillation
	LAD	3	6 m		
11	LAD	7	20 m	0.55	Death from cardiac standstill
14	LAD	5	20 m	0.58	Ventricular fibrillation. Discolored myocardium suggesting early infarction; no necrosis microscopically
16	LAD	12	17 d	0.88	Ventricular fibrillation immediately after complete occlusion at second operation. No myocardial fibrosis or necrosis
	LAD	0	0		
19	LAD	9	12 m	0.39	Ventricular fibrillation
20	LAD	9	15 m	0.48	Ventricular fibrillation
24	LAD	27	20 m	—	Ventricular fibrillation. Discolored myocardium suggesting early infarction. Edema of myocardium microscopically
25	LAD	0	6 m	—	Ventricular fibrillation
29	RC	22	6 h	0.64	Early infarction; acute necrosis microscopically
31	RC	17	21 d	—	Cardiac standstill immediately after complete occlusion at reoperation
	RC	0	0		
33	RC	13	18 m	—	Ventricular fibrillation. Discolored myocardium suggesting early infarction; no necrosis microscopically
35	RC	0	3 h	—	Discolored myocardium suggesting early infarction; edema of septum, no necrosis microscopically
37	RC	13	14–21 h	—	Discolored myocardium suggesting early infarction; edema of myocardium microscopically
38	RC	0	13 m	—	Ventricular fibrillation
44	RC	0	45 m	—	Complete occlusion from intimal tear; edema of septum microscopically
53	RC	100	7 d	—	Loose nonconstricting tie at original operation; subsequent complete occlusion at same point followed by cardiac standstill and death
	RC	0	1 m		
55	RC	0	5 m	—	Ventricular fibrillation
			C. Experiments with Marked Narrowing in which Animals Died of Noncardiac Causes		
8	LAD	32	48 h	—	Respiratory death
12	LAD	21	7 d	—	Hemorrhage at reoperation
13	LC	7	5–10 h	—	Animal found dead
17	LAD	15	35 m	0.68	Coincidental infectious disease
22	LC	25	35 m	0.46	Respiratory death; no myocardial necrosis microscopically
23	LAD	22	3 h	—	Respiratory death; no myocardial necrosis microscopically
27	RC	40	3 d	0.39	Animal decerebrate following operation
40	RC	8	14 d	0.48	Sacrificed. Myocardium normal microscopically

KEY:

LAD—Left anterior descending coronary artery.
LC—Left circumflex coronary artery.
RC—Right coronary artery.
d—Days.
h—Hours.
m—Minutes.

on the basis of our other results were not visualized.

Hearts in which Intercoronary Anastomoses Were Produced Experimentally

Hearts with Intercoronary Anastomoses: Functional Adequacy Not Tested: In 4 animals (table 3, *A*) with survival times of sixteen to twenty-five days after narrowing of the right coronary artery, anatomic evidences of abundant collateral circulation were observed. The lumens had been reduced to 10 to 21 per cent of the original cross-sectional area. In Animal 30, a branch of the right coronary artery proximal to and distant from the point of previous narrowing was completely occluded two days before sacrifice. The anastomotic connections visualized were distal to the original narrowing. No such connections were present in relation to the recently occluded branch. It is of interest that although the collateral channels in this animal were widespread, they were nevertheless tailored specifically to the narrowing which had evoked them. They did not develop indiscriminately or generally in the coronary tree and were not available as preformed anastomoses to obviate the effects of the new occlusion in the distant branch of the right coronary artery. Time is required for the development of such communications in the area immediately about an occlusion.

Hearts with Intercoronary Anastomoses which Were Functionally Inadequate: In the second group of experiments (table 3, *B*) definite intercoronary anastomoses were visualized, but death occurred at the second or third operation, when the previously narrowed artery was suddenly and completely occluded. In the animal surviving three hours after the initial narrowing (Animal 7) there was the faintest trace of injection mass derived from collateral pathways in the occluded artery. Somewhat more filling with mass from collateral vessels was present in the animal surviving fifty-two hours (Animal 10). In the animal (Animal 15) surviving seven days, abundant collateral circulation was demonstrated in the complete filling of the territory of the occluded vessel by mass from the other coronary arteries.

It may be stated, therefore, that collateral vessels of the size disclosed by the Schlesinger technic may rarely begin to appear within hours, and occasionally after days, but that these collateral vessels in their early development are inadequate to sustain the heart after a superimposed sudden complete occlusion.

Hearts with Intercoronary Anastomoses and Survival after Complete Occlusion: In our experience (table 2, *B*), no pig had survived sudden complete occlusion of the left anterior descending or right coronary artery. In 3 animals (Animals 32, 36, and 43, table 3, *C*) in which a major coronary artery had been narrowed and the animals permitted to survive thirteen to twenty-five days, the previously narrowed artery was suddenly and completely occluded one to two days prior to sacrifice. Abundant intercoronary communications were displayed post mortem in each heart (fig. 1, *C*). The fact that, in contrast to the experiments of tables 2, *B* and 3, *B*, these animals endured acute coronary occlusion, permits one to conclude that the collateral circulation demonstrated anatomically was functionally serviceable in protecting the heart and thereby enabled the animals to survive. In 2 additional instances (Animals 41 and 42) in which complete occlusion occurred gradually over a period of twelve to thirteen days, similar abundant intercoronary anastomoses were demonstrated.

In none of the hearts of table 3, *C* were gross evidences of acute myocardial infarction discernible. This was particularly significant in Animals 32, 36, and 43 in which complete occlusion was imposed one to two days before sacrifice. Moderate amounts of microscopic necrosis were present in two of these hearts; in the heart of Animal 32, there was no microscopic necrosis at all. Estimation of the amount of fibrosis by microscopic examination and by determination of the collagen content of the left ventricular muscle showed a slight increase or no change (table 3, *C*). These observations are further evidences of the functional serviceability of the collateral circulation produced experimentally in these animals.

Evidence of Extracardiac Collateral Circulation: Although not a primary objective of these experiments, it was of interest to observe whether extracardiac collateral vessels devel-

TABLE 3.—*Experiments in Which Interarterial Coronary Anastomotic Connections Were Produced*

Animal Number	Artery Constricted	Size Lumen after Ligation (% Original Area)	Time before Death	Anastomoses		Collagen (Grams %)	Remarks
				Location	Degree*		
A. Experiments in which Functional Adequacy of Anastomoses Was not Tested							
28	RC RC	15 0	21 d 8 m	LC-RC	++	0.89	Complete occlusion for 8 minutes without arrhythmia or other cardiac effect before sacrifice. No myocardial fibrosis or necrosis microscopically
30	RC RC Br	21 0	25 d 2 d	LAD-RC LAD-LC	+++	0.73	Occluded branch of RC not injected. Moderate amount of fibrosis and necrosis microscopically
34	RC	11	24 d	LAD-RC LAD-LC	+++	0.72	No myocardial fibrosis or necrosis
39	RC RC	10 0	16 d 2½ m	LAD-RC	++	0.74	Complete occlusion for 2½ minutes without arrhythmia or other cardiac effect before sacrifice
B. Experiments in which Anastomoses Were Functionally Inadequate							
7	LAD LAD	19 0	3 h 16 m	RC-LAD	+	—	Ventricular fibrillation immediately after complete occlusion with death in 16 minutes
10	LAD LAD LAD	53 16 0	52 h 28 h 3½ h	RC-LAD	++	0.65	Acute myocardial infarction.
15	LAD LAD	15 0	7 d 5 m	RC-LAD RC-LC	+++	0.69	Ventricular fibrillation immediately after complete occlusion. Single area of necrosis measuring 75 micra in diameter
C. Experiments with Interarterial Anastomoses and Survival after Complete Occlusion							
32	RC RC	27 0	25 d 1 d	LAD-RC LC-RC	+++	0.66	No myocardial fibrosis or necrosis
36	RC RC	10 0	22 d 2 d	LAD-RC LC-LAD	+++	0.59	Slight fibrosis and moderate amount of necrosis microscopically
41	RC	0	13 d	LAD-RC RC-RC	+++	0.74	Artery narrowed at operation was found completely occluded 13 days later by fibrosis about ligature, indicating long-standing occlusion. Slight amount of fibrosis and necrosis microscopically
42	RC	0	12 d	LC-RC	+++	0.78	See remarks #41. Moderate amount of necrosis microscopically
43	RC RC	— 0	13 d 1 d	LAD-RC LAD-LC LC-RC	+++	0.75	Slight fibrosis and moderate amount of necrosis microscopically

* Graded on scale of + to +++

KEY:

LAD—Left anterior descending coronary artery.
LC—Left circumflex coronary artery.
RC—Right coronary artery.
Br—Branch of main coronary artery.
d—Days.
h—Hours.
m—Minutes.

oped particularly in those hearts with adherent pericarditis. In seven experiments (Animals 30, 32, 34, 39, 41, 42, and 43) definite pericardial adhesions were present near or over a portion of the myocardium in the territory of the narrowed or occluded coronary artery. Despite

collateral vessels in the vicinity, in no instance did the injection mass traverse the pericardial adhesions.

Discussion

The question whether intercoronary anastomoses exist has been the subject of vigorous discussion for many decades. Intense interest in this problem has been provoked not only because of its scientific importance but also because of the direct clinical implications for our understanding of angina pectoris and acute myocardial infarction. The impossibility of measurements of the coronary flow in man during life and the manifold variations in technics of post mortem studies in man and in experimental conditions in animals have led to conflicting and even contradictory opinions.

Failure to appreciate the differences in the architecture of the coronary tree in man, in dog, and other experimental animals; the variations in the observations resulting from diverse experimental conditions and technics; lack of agreement regarding the terminology employed; the paucity of evidence regarding the functional significance of the anastomoses observed, and, at times, neglect in discriminating between the normal and the changes induced by disease—all these have from time to time served to confuse the issue. To interpret the relation of our results to the work of others, some of these questions require brief discussion.

The Types of Coronary Arterial Anastomoses: Extracardiac anastomoses of the coronary arteries repeatedly have been observed with the vessels leading to adjacent structures, i.e., the venae cavae, the aorta, the pulmonary vessels, the reflections of the parietal pericardium, and across the adhesions in the presence of pericarditis.[10–19] The functional significance of these communications under normal circumstances and their usefulness in providing accessory channels of blood flow in the presence of coronary arterial occlusion have been studied by many investigators.[18–36] No anastomotic communications across pericardial adhesions of the size disclosed by lead-agar injection mass were observed in our experimental studies, despite the favorable fact that adhesions developed immediately after coronary narrowing or occlusion directly over the infarcted or ischemic myocardium. Our previous studies with the Schlesinger injection mass in man have likewise failed to disclose collateral channels across pericardial adhesions formed after acute myocardial infarction and pericarditis.

Coronary-luminal communications have been considered as a source of nourishment for the myocardium by many observers since their demonstration by Vieussens[37] and Thebesius.[38] These vessels presumably are connections in the intramural coronary circulation between the chambers of the heart and the various subdivisions of the coronary arterial tree (arterioles, capillaries, venules, and sinusoids).[10–12, 14, 23, 34, 39–81] They have not been demonstrated by the lead-agar mass employed by Schlesinger in the normal or abnormal hearts of man, dog, or pig. Nor have other communications such as coronary arteriovenous shunts[81–84] been seen by us.

Intercoronary arterial anastomoses have engaged the main interest of investigators because of their serviceability after occlusion of a coronary artery in supplying blood from a neighboring unaffected artery to the capillaries and tissue of the potentially infarcted area.

Normal Intercoronary Anastomoses as Demonstrated Anatomically: Species Differences: In 1669, Richard Lower[39] stated that "... the vessels which carry blood to the heart ... come together again, and here and there communicate by anastomoses." Anatomic investigations in men and animals[7, 10–13, 17–19, 31, 32, 38, 41, 42, 46, 50, 56, 59, 81, 83, 85–108] with injection materials such as water, air, suet, wax, dyes, inks, mercury, bismuth, lead, and radioactive phosphorus to supplement dissections of the heart confirmed Lower's finding of intercoronary arterial anastomoses and led to their general acceptance. Occasional assertions to the contrary were expressed,[82, 109–114] largely because variations consequent to species differences, differences in health and disease, as well as differences in technic were not appreciated.

Our own observations[6, 115] clearly indicate that in the normal heart of the dog, pig, and man, fine interarterial coronary communications exist. Colored watery solutions injected

into one coronary artery promptly appear in the other coronary arteries and their branches. Similarly, Prinzmetal and co-workers[108] have noted that watery solutions of fluorescein appear in different arteries after injection into one of the coronary vessels.

Injection materials may be used which do not regularly fill the capillary bed. The lead-agar mixture utilized in the Schlesinger technic regularly fills vessels down to 40 microns and irregularly penetrates to vessels from 40 to 10 microns in diameter. The above diameters of the arterial system apply to the vessels as seen in fixed tissues in stained microscopic preparations; to apply to vessels in the fresh or natural state, the measurement would be approximately double.[116] The mass does not fill the capillary bed or appear in the venous system. These findings have been confirmed, in general, by others.[107, 117, 118] In approximately 15 per cent of normal human hearts, the interarterial communications are of sufficient size to be demonstrated by the lead-agar mass, that is, a continuous injected pathway was visible grossly between arterial branches, or the colored injection mass passed from one arterial tree to another by way of invisible connections.[116]

In contrast to our findings in man, interarterial coronary anastomoses were seen in almost all dog hearts. In many dog hearts, the interarterial communications are visible to the naked eye, i.e., larger than 60 to 80 microns in diameter, and correspond to vessels arteriolar or arterial in nature. It was this finding that led us to abandon the dog as the subject for the experimental induction of such anastomoses.

The increased incidence and caliber of the interarterial anastomoses in the normal dog heart[7, 31, 32, 89, 94, 98, 102, 107] as compared to the human must be borne in mind in the critical evaluation of the large volume of experimental work on dogs. The inconstancy of experimental infarction in occurrence and size, noted in the work of others, is explicable on those grounds.[93, 119–122] In the dog, additional factors in the variable effect of occlusion of the left anterior descending coronary artery are variations in the gross architecture of the coronary tree. The septum is supplied anteriorly in the dog by a single large vessel[7, 94, 102, 110, 123] arising at a variable location from the left anterior descending coronary artery; in man the septum is supplied by a brushwork of small vessels from the left anterior descending artery. Ligation of the left anterior descending coronary artery in the dog would have a greatly different effect upon the heart muscle depending upon whether or not this septal branch was occluded. Furthermore, in the dog, the left circumflex coronary artery is always relatively long in comparison to the right coronary artery and gives rise to the posterior descending branch. This pattern corresponds to the most infrequent type seen in man.[97, 98, 112, 124, 125]

The pig was chosen as the subject of this investigation because interarterial communications were witnessed in only 2 animals of 55 with the Schlesinger technic (table 1). In these two hearts they were superficial, few in number, and could be distinguished readily from those produced experimentally. The uniform production of acute infarction or, more frequently, sudden death from cardiac standstill or ventricular fibrillation following coronary occlusion is in accordance with these anatomic observations. Furthermore, the right coronary artery is relatively long in the pig and the posterior descending branch arises from it rather than from the left circumflex coronary artery. In this way, the pig heart corresponds to the most common type "right coronary preponderant pattern" found in man. Because of its relative predominance, ligation of the right coronary artery also resulted uniformly in extensive infarction or death in the pig.

Functional Significance of the Normal Intercoronary Anastomoses: The physiologic significance of the normal interarterial connections and the circumstances which may lead to their magnification have been the subject of intensive study.[4, 5, 19, 27, 31, 32, 46, 50, 59, 91, 94, 107, 110, 111, 113, 114, 119, 126–166] To the anatomist, an end artery is an artery which does not communicate with other arteries through any anastomotic connection, so that its capillary bed receives blood from no other artery. To the physiologist, an end artery is an artery which alone supplies sufficient blood to an area to maintain its function and integrity; when this vessel is occluded the dependent area undergoes loss of function

or necrosis because other arteries do not supply the given area sufficiently. These two definitions differ widely from each other; anatomic studies in other parts of the body have repeatedly demonstrated interarterial communications among vessels which are clearly end arteries physiologically. Wiggers[167] has cogently remarked that "... it has long been accepted that the coronaries are terminal arteries, for when plugged by emboli or thrombi in man or when artificially occluded in animals an infarct results. The rapid necrosis of cardiac tissue could scarcely occur, were adequate anastomoses present." The failure of the supplied area to contract within one or two minutes following sudden occlusion and the electrocardiographic evidence of immediate injury are further manifestations of functional inadequacy, as is indeed the common catastrophic clinical experience with patients suffering from acute coronary occlusion. Experimentally in the dog, the area peripheral to the coronary ligature becomes swollen, cyanotic, and engorged, and the veins appear full. Prinzmetal and associates[108] have recently reported that the amount of blood in such stagnant areas may be equal to two-thirds or more of the normal.

Although the intercoronary anastomotic channels in the normal heart do not prevent infarction after sudden occlusion, they do have some functional significance. It has been observed[59, 93, 101, 119, 153, 154, 168] that following experimental or clinical acute occlusion of a coronary artery, the area of infarction is smaller than the entire territory of the distribution of this artery and its branches. Indeed, in some dogs, gross infarction does not appear at all because of the richer intercoronary connections.[120, 121] Furthermore, following the acute occlusion of a coronary artery in the normal dog heart, cannulation of the cut artery peripheral to the tie reveals retrograde flow amounting to as much as 7.2 cc. per minute.[169, 170] By gasometric analysis, this blood was found to be arterial in nature and, therefore, must have been derived from precapillary interarterial connections.

Prinzmetal and his associates[108] injected radioactive erythrocytes, tagged with P^{32} (Na_2HPO_4), at various times in relation to ligation of the left anterior descending artery of the dog. Several moribund patients were also studied. Surface measurements of the beta radiation were converted by calculation into amounts of blood per gram of tissue. The calculation that the subepicardial ischemic myocardium contains as much blood as neighboring uninfarcted portions makes one hesitant to interpret the measurements into terms of blood flow. Furthermore, their ingenious technic is complex and contains some variables, such as, the amount of radiation contributed by the blood in the surface veins, possible capillary extravasations incurred by infarction[166] and rapid freezing, and the diffusibility of P^{32} from the red cells into the plasma during even short periods of time, particularly if hemolysis has occurred. As pointed out by these investigators, the usual presence of cyanosis despite blood circulating through the ischemic area, indicates that the normal interarterial communications permit less blood flow in such areas than in other portions of the myocardium. They further observed by means of watery solutions of fluorescein that, as in the normal heart, the fine communications permit entrance of the dye to all parts of the heart including the infarcted region beyond the tie. The subendocardial portions of the heart contained less blood than normal in the ischemic region. In applying such experimental results to man, the relative abundance and magnitude of the collateral vessels observed in the normal dog must be borne in mind.

Interarterial Anastomoses in Relation to Coronary Narrowing and Occlusion in Man: Only approximately 15 per cent of normal human hearts reveal interarterial communications large enough to be disclosed by the Schlesinger lead-agar mass; when found, they are few in number. In contrast, 98 per cent of hearts with occluded arteries reveal collateral channels which are more numerous, occasionally visible to the naked eye, and of great functional significance. This has been demonstrated in hearts in which, despite complete occlusions, the potentially infarcted myocardium has been free of fibrosis or other structural abnormality.[4, 5, 116]

When narrowing progresses gradually, complete occlusion in one or even in all three main

coronary arteries may be compatible with continued life.[4, 5, 20, 27, 59, 66, 71, 91, 101, 117, 118, 127, 134, 136, 146, 149, 168, 171, 172] Most patients with such hearts experience angina pectoris or congestive failure. Injection of these hearts demonstrates an extraordinarily rich network of anastomoses. All semblance of end arteries is lost.

Experimental Augmentation and Functional Significance of Anastomoses Following Coronary Narrowing or Occlusion: Bed rest after acute myocardial infarction serves a twofold purpose: (1) it reduces the work of the heart, favors healing of the infarct, and lessens liability to cardiac rupture, (2) an opportunity is provided for development of a more adequate intercoronary collateral circulation. It is consequently of practical as well as of theoretical importance to know the length of time required to establish such communications after sudden acute narrowing of the coronary artery and to learn whether the communications developed after a given interval of time are functionally adequate to protect the myocardium from the dire effects of the acute occlusion. As already stated, studies of human hearts cannot yield clear answers to these questions.

Experimental studies by others have disclosed interesting and significant data. Acute or gradual occlusion of the coronary artery in the dog is associated with enlargement of collateral vessels and does not necessarily result in infarction of the myocardium.[31, 32, 120, 121, 163–165] Following acute coronary occlusion in the dog, retrograde flow, derived mainly from other arteries, increases within a few hours and progresses steadily for some hours thereafter.[170] In animals surviving acute or gradual coronary occlusions for long periods (thirty-six to three hundred and sixty-five days), the peripheral coronary pressure is greatly increased, at times approaching the prevailing aortic pressures, and the retrograde flow coming from the peripheral end of the occluded artery may amount to 105 cc. per minute (values immediately after occlusion up to 1.5 cc. per minute).[165] Furthermore, after a minimum of seven weeks, the ischemic areas are able to contract. As the authors point out, it is highly improbable that retrograde flows of such magnitude, as were obtained experimentally against atmospheric pressure, exist in the intact heart when the occluded artery is not permitted to bleed. Likewise, the animals studied represent a select group of those which were able to survive acute complete occlusion. They may well be those which possessed natural interarterial connections larger than most. The more abundant collateral circulation in the dog heart compared to man renders application of these results to human experience somewhat uncertain.

These experimental studies have concerned themselves mainly with the effects of sudden complete occlusion or have simply demonstrated the development of collaterals after gradual narrowing. The degree of narrowing and the time interval necessary for the development of collaterals and the functional significance of such collaterals at various stages of their development were not determined.

The relation of angina pectoris, coronary failure, and acute myocardial infarction to coronary arterial narrowing and occlusion and the development of collateral vessels in human hearts have been the subject of previous communications by us.[4, 5] Complete occlusion usually occurs in a previously narrowed artery. Consequently, the present studies of the sequence of events after graded and measured degrees of narrowing afford additional insight into the significance of our data in man. The results of our experiments (tables 1, 2 and 3) clearly demonstrate that narrowing of an artery to 10 to 27 per cent of the original cross-sectional area is commonly followed by the development of the interarterial anastomoses of the size disclosed by the Schlesinger technic (table 3). Acute narrowing to less than 13 per cent of the original lumen area generally leads to death of the animal (table 2, *B*) whereas only slight narrowing did not stimulate anastomoses during the three weeks of survival prior to sacrifice. Freely communicating anastomoses rarely appeared within hours or days but were abundant after two weeks. The development of such abundant anastomoses was necessary for the protection of the myocardium from sudden, superimposed complete occlusion.

The exact anatomic characteristics of these communications and the mechanism of their development have not been studied. The experi-

mental results clearly demonstrate, however, that anastomoses may develop in the absence of any myocardial necrosis or fibrosis. Factors consequent to the narrowing which may promote the development of anastomoses include the following: the opening of pre-existing or the formation of new collaterals by metabolites, directly or by reflex action, and by differential pressures. It is reasonable that the reduced pressure in a coronary artery distal to the point of narrowing or occlusion results in a pressure gradient between such areas and the neighboring unaffected artery, thereby opening up and dilating the pre-existing small communications. This concept was clearly expressed by Lower[39]: "... Hence, it sometimes happens that, when the lumen of some artery has been too long obstructed or ligated, the blood busies itself in opening a wider channel for its passage in this vessel, must drive and buffet all the more into the next ones, until it has considerably dilated them to give itself room."

Contrary to the current tendency to advise early ambulation, the slow development of these collateral channels emphasizes the importance of bed rest and reduced activity for many weeks after acute myocardial infarction. Ample evidence exists that reduced cardiac work favors healing of the infarct, reduces the extent of myocardial damage, lessens liability to rupture, and provides time for the development of these anastomotic channels. Similar considerations would seemingly apply to patients in whom angina pectoris suddenly appears or in whom the frequency or intensity of the attacks suddenly increases. If one can exclude temporary factors causing an increased demand for blood (fever, anemia) or physiologic reduction in coronary flow (shock, tachycardia), the sudden inadequacy of blood supply may be ascribed to structural organic narrowing or occlusion. Such sudden imbalance of coronary circulation must always be viewed with gravity, for any new reduction in coronary flow may result seriously in extensive myocardial necrosis if excessive demand is placed upon the heart before equilibrium is re-established by full development of anastomotic pathways. On the other hand, the slow development of a richer anastomotic circulation may be responsible for the occasional clinical improvement of patients with angina pectoris, the collateral channels acting to offset the narrowing or even occlusion which has occurred.

Summary and Conclusions

1. The speed with which coronary interarterial anastomoses develop and the degree to which they protect the myocardium from the effects of coronary arterial narrowing and occlusion have been studied.

2. In contrast to human hearts, the hearts of dogs almost always show relatively large interarterial connections normally; the experiments were therefore performed on pigs.

3. In 53 of 55 normal pig hearts, no intercoronary anastomotic connections of the size disclosed by the Schlesinger technic were visible. In 2 hearts fine superficial intercommunicating twigs, readily distinguishable from those produced experimentally, were seen.

4. Sudden complete occlusion or sudden marked narrowing to less than 13 per cent of the original cross-sectional area of the right coronary artery in its midportion, or of the left anterior descending artery near its origin, was generally incompatible with survival; ventricular fibrillation or cardiac standstill usually occurred within twenty minutes.

5. In three experiments in which moderate narrowing to 15 to 19 per cent of the original lumen was produced, slight evidences of collateral circulation were demonstrated after survival periods of three hours, fifty-two hours, and seven days respectively, but this collateral circulation in its early development was functionally inadequate to protect the heart from the effects of suddenly superimposed complete occlusion of the artery.

6. In nine of the twelve experiments in which the animal survived twelve or more days after moderate narrowing, rich anastomotic communications between the major coronary arteries were demonstrated by the injection technic.

7. Collateral coronary circulation developed in these 9 animals was shown in 5 to be functionally significant, for the heart survived suddenly superimposed, or gradually developing complete obstruction one or more days before the animal was sacrificed.

8. In none of the 5 hearts with functionally adequate collateral vessels were gross evidences of acute myocardial infarction discernible. Estimation of the amount of microscopic fibrosis and necrosis showed none to a moderate increase. The collagen content of the left ventricular muscle showed a slight increase or no change, indicating again the functional serviceability of the collateral circulation produced experimentally in these animals.

9. In seven experiments, definite pericardial adhesions were present near or over a portion of the myocardium in the territory of the narrowed or occluded coronary artery. Despite collateral vessels in the vicinity, in no instance did the injection mass traverse the pericardial adhesions.

10. The physiologic and pathologic significance of the collateral intercoronary communications and the clinical implications in coronary artery disease are discussed.

11. Contrary to the current tendency to advise early ambulation, the slow development of these collateral channels emphasizes the importance of bed rest and reduced activity for many weeks after acute myocardial infarction. Similar considerations would seemingly apply to patients in whom angina pectoris suddenly appears or in whom the frequency or intensity of the attacks suddenly increases.

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Paroxysmal Ventricular Tachycardia: A Study of One Hundred and Seven Cases

By CHARLES A. ARMBRUST, JR., M.D., AND SAMUEL A. LEVINE, M.D.

A review is presented of 107 cases of paroxysmal ventricular tachycardia. In the majority it was associated with acute coronary thrombosis or coronary sclerosis, in some with rheumatic valvular disease, and in others with no organic heart disease. It is generally critical and demands careful attention. Occasional cases are overlooked because only one heart sound is present for each cardiac cycle and the heart rate is misjudged to be one-half the actual rate. The outlook often is serious if the condition is not effectively treated. Therapy generally is successful in controlling the arrhythmia. The most valuable drug is quinidine. Other medications are magnesium sulfate, atropine, potassium salts, and possibly morphine.

PAROXYSMAL ventricular tachycardia is one of the less common types of paroxysmal rapid heart action. In spite of its rarity, prompt diagnosis and treatment are most important because often the patient's life is at stake and with proper therapy the results may be excellent. The arrhythmia occurs predominantly in patients with serious organic heart disease and this, in addition to the effect of the rapid ventricular rate, makes it imperative that the attack be terminated as soon as possible if a fatal outcome is to be averted.

Lewis[1] reported the first case of ventricular tachycardia. His patient was a seaman who had repeated premature ventricular contractions occurring singly and in runs of as many as 11 beats. Shortly after Lewis' publication in 1909, reports[2–4] of isolated instances of this arrhythmia appeared which were followed by reports of larger series and more complete reviews.[5–8] Lewis[9] produced ventricular tachycardia in dogs by ligating the coronary arteries and Robinson and Herrmann[10] called attention to the relationship of paroxysmal ventricular tachycardia to coronary occlusion in man. Scott,[11] in 1921, was successful in controlling this arrhythmia by the use of quinidine administered orally. There was 1:1 retrograde conduction to the auricles and no evidence of organic heart disease. The present study of 107 cases is reported with the hope of clarifying some of the problems of diagnosis, prognosis, and treatment encountered in patients with this disorder.

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MATERIAL

All cases of paroxysmal ventricular tachycardia occurring in the Peter Bent Brigham Hospital and the private practice of one of us (S. A. L.) from 1915 to 1948, inclusive, have been studied. Sixteen of these cases have been reported previously.[12–16] The total number of episodes of ventricular tachycardia observed in this study of 107 subjects was 131. The youngest patient was 13 years of age and the oldest 83 years. The age distribution by decades is shown in figure 1. The average age was 54.8 years. Seventy-one patients were males and 36 were females. The types of underlying heart disease are shown in table 1, and it will be noted that

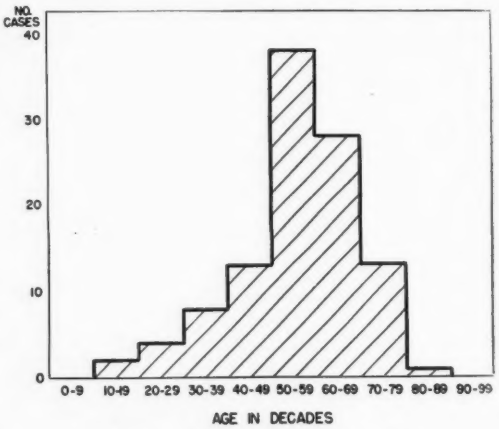

FIG. 1.—Age Distribution of Cases

TABLE 1.—*Types of Underlying Heart Disease*

1. Coronary Artery Disease	79
2. Rheumatic Heart Disease	9
3. No Heart Disease	13
4. Miscellaneous Group	
(A) Wolff-Parkinson-White Syndrome	5
(B) Congenital Heart Disease	1

coronary artery disease was present in 74 per cent of the patients. The duration of the attacks varied from a few seconds to twenty-three days. Eighty-two patients had persistent attacks (hours to days) and 25 had intermittent attacks (seconds to a few minutes). The ventricular rate during the episodes varied from 138 to 292 with one exception; in one patient the rate was 115.

Clinical Diagnosis

The bedside findings which suggest the clinical diagnosis of paroxysmal ventricular tachycardia have been described by Levine[17,19] and Strong and Levine.[18] These consist of a changing intensity of the first heart sound at the apex, a slight irregularity of the ventricular cycle length, and the failure of vagal stimulation to produce any effect on the tachycardia.

A changing intensity of the first sound was noted in forty-three episodes. This sign will be detected only on careful auscultation and is not present in patients who have concomitant auricular fibrillation or in those in whom there is 1:1 retrograde conduction. In the rare instance in which 2:1 retrograde conduction to the auricles takes place one might expect to find alternation in the intensity of the first sound. The mechanism of production of the changing first sound is thought to be dependent on the changing relationship between auricular and ventricular contraction, similar to that which occurs in conjunction with complete heartblock.[19] Excluding the patients with auricular fibrillation, a changing intensity of the first sound was noted in approximately 50 per cent of the patients in this series.

In the common type of paroxysmal auricular tachycardia the cycle length is perfectly constant, whereas in ventricular tachycardia slight but detectable irregularities in the cycle length may be observed in an appreciable number of instances. The slight irregularities in rhythm in ventricular tachycardia can easily be overlooked unless auscultation is carried out carefully. Cooke and White[7] on the other hand found thirteen of fifteen tracings of definite and prolonged paroxysms of ventricular tachycardia to be perfectly regular. Cooke and White[7] also found that irregular rhythm was most likely to occur during short paroxysms and in patients with auricular fibrillation. Williams and Ellis[8] found only 4 of 24 patients with the persistent type of tachycardia to have an obvious irregularity of the rhythm. In the 107 episodes of the persistent type of tachycardia in this series, in 32 per cent the rhythm was slightly irregular, while in 76 per cent of the intermittent type a similar type of slight irregularity was manifest. In considering the slight irregularity that is seen in paroxysmal ventricular tachycardia it must be clear that the actual heart rate can be quite constant over long periods of time. It is the length of contiguous cycles that may change. The difference may not be more than 0.03 second though occasionally it is much greater and may not occur but once in many cycles. The ear is able to appreciate these slight variations in cycle length. In contrast, the contiguous cycles in the common type of paroxysmal auricular tachycardia rarely vary more than 0.01 second in length.

Paroxysmal ventricular tachycardia does not respond to vagal stimulation. This finding is helpful in the differentiation of ventricular from paroxysmal auricular tachycardia, auricular flutter, and sinus tachycardia.

Gallarvardin[20] described changes in the jugular pulse wave in patients with ventricular tachycardia. Further observations of the jugular pulse during the arrhythmia have been reported by Prinzmetal and Kelley.[21] In ventricular tachycardia the auricular rate is generally slower than the ventricular rate and the pulsations of the auricles at this slower rate may be visible in the jugular vein. In addition, occasional prominent jugular waves will appear during cycles when the auricles are contracting while the ventricles are in systole. Such findings may be particularly helpful in those patients in whom P waves are not visible in the electrocardiogram. The abnormal jugular pulsations will be absent in subjects in whom there is no change in the intensity of the first heart sound, that is, in those with auricular fibrillation and 1:1 retrograde conduction.

There is one additional unusual auscultatory phenomenon that merits discussion, particularly since it has not been hitherto described. There were three instances in this series in which only one heart sound could be heard

with each cycle. In 2 patients this resulted in the heart rate being misinterpreted by some observers as being one-half the actual rate. In one of these patients, the sounds alternated in intensity so that they closely resembled the normal sounds. It was difficult at the bedside to tell whether the rate was 115 with two sounds to a beat or 230 with only one sound. This could not be determined from the radial pulse since the patient was pulseless and the blood pressure was not obtainable. The electrocardiogram quickly revealed the fact that the ventricles were beating at a rate of 230. It is of interest that in this case two physicians who had been seeing the patient for some hours had overlooked the tachycardia and thought the heart rate was "about one hundred." Such experiences must be more frequent than has been realized as we have seen other instances of paroxysmal rapid heart action in which only one heart sound could be heard with each cardiac cycle.

In summary, one may state that there are bedside methods available which will enable the physician to suspect the diagnosis of paroxysmal ventricular tachycardia in most cases and even to make a fairly definite diagnosis in many instances without the aid of the electrocardiograph.

Electrocardiographic Diagnosis

The criteria for the electrocardiographic diagnosis of ventricular tachycardia were first proposed by Robinson and Herrmann.[10] They emphasized three features. The first is the detection of auricular complexes (P waves) occurring independently and at a slower rate than the ventricular rate. The second is the presence of ventricular complexes that are abnormal in form and different from those observed in the same patient when the paroxysm is not present. The third is the finding of isolated ectopic ventricular complexes before or after a paroxysm that have the same form as the ventricular complex during the paroxysm.

The presence of P waves may be difficult to detect in the standard limb leads and therefore special auricular leads may be of value in their demonstration.[8] If the condition of the patient is not too serious, esophageal leads taken in the auricular region may be helpful.

The abnormal ventricular complexes in themselves are not sufficient to make the diagnosis, as there may be aberration of the ventricular complexes due to the rapid rate alone.[10] Also auricular tachycardia, auricular fibrillation, auricular flutter, and nodal tachycardia with aberrant ventricular conduction or with permanent bundle branch block may simulate ventricular tachycardia.[22] The concomitant presence of auricular fibrillation and paroxysmal ventricular tachycardia which occurred in 20 of the cases adds further difficulties in diagnosis.

Cooke and White[7] noted that ectopic ventricular beats exactly similar in type to those of the paroxysm may be very difficult to find and that complexes almost alike are adequate to aid in the diagnosis. It is of interest that these authors have reported other cases in which auricular premature beats preceded and followed the paroxysms of ventricular tachycardia. They have also observed that the occurrence of paroxysms of abnormal ventricular complexes, regular and more rapid than the previous rate during auricular fibrillation, is diagnositic of ventricular tachycardia.

Patients with Coronary Artery Disease

In our series, in 79 cases (74 per cent) coronary artery disease was the cause of the underlying heart disease. The diagnosis of coronary artery disease was restricted to those patients who had angina pectoris or myocardial infarction, either acute or old. A number of the patients in this group had, in addition, hypertensive cardiovascular disease, but no distinction has been made here between the hypertensive and nonhypertensive. In 44 patients the attacks occurred following an acute myocardial infarction. The youngest patient was 31 years of age and the oldest 83 years. There were 55 men and 24 women. The attacks of tachycardia were of two types, persistent or intermittent. The latter were short paroxysms of tachycardia lasting seconds or minutes which ceased spontaneously or were controlled readily in most cases by therapy. There were 18 patients of the group with coronary artery disease who had intermittent paroxysms. The persistent type of

attack, of which there were seventy-six instances presents the more difficult therapeutic problem. The episodes, as can be seen in figure 2, tend to occur most frequently with the onset of acute myocardial infarction or during the first two weeks after the acute infarction. The attacks of tachycardia were regarded as occurring with the onset of an acute myocardial infarction when they were noted during the first six hours after the first evidence of coronary pain. It is not possible to determine how many subjects if any, developed the rapid heart rate directly with or a few seconds after the first

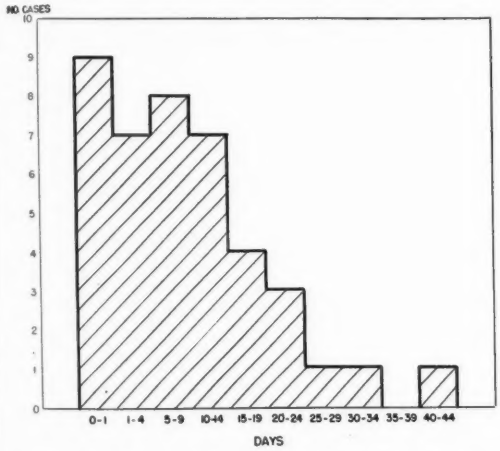

FIG. 2.—Onset of Paroxysmal Ventricular Tachycardia after Acute Infarction.

evidence of heart pain. If the attack of tachycardia occurs at the same time as the acute infarction there may be some difficulty in either confirming or excluding the diagnosis of the underlying infarct. It is quite well known that paroxysmal rapid heart action of any type can result in chest pain, fever, leukocytosis, fall in blood pressure, and even subsequent electrocardiographic changes without any myocardial infarction.[23,24] An added difficulty is that the shock state resulting from the tachycardia may be followed by a myocardial infarction, such as occurs in association with shock following hemorrhage or surgical operation.

Patients may have single or multiple attacks of ventricular tachycardia. The control of multiple attacks depends on the use of varying doses of quinidine prophylactically. There were 10 patients with coronary artery disease who had multiple attacks of ventricular tachycardia while under observation and 17 additional patients who gave a history of multiple episodes. The attacks in 3 of these patients were particularly interesting.

One patient had his first attack of paroxysmal ventricular tachycardia on the twenty-sixth day after an acute myocardial infarction. In the ensuing sixteen days he had twelve recurrent episodes. Following each attack reversion to normal rhythm occurred after a single dose of quinidine sulfate, either 0.6 Gm. given intravenously or 1.0 Gm. orally. This patient then had an uneventful recovery and is alive and working at the present time, two and one-half years following the last episode.

The second patient, a 55 year old Negro, had an acute myocardial infarction complicated by ventricular tachycardia in 1939. From 1939 to March 1949 he had 111 episodes of paroxysmal rapid heart action. In five observed attacks the arrhythmia was identified as ventricular tachycardia and each episode was arrested by quinidine therapy. It is reasonable, therefore, to assume that all the other attacks were of similar origin. These attacks have recurred in spite of the prophylactic use of quinidine and potassium salts but the patient has continued his work as a janitor.

The third patient, a 58 year old white man, had an acute myocardial infarction in 1943 complicated by ventricular tachycardia. From December 1943 to the present time he has been treated in the hospital for eight episodes of ventricular tachycardia and has controlled many attacks at home by taking quinidine orally. He is working at the present time.

These 3 cases are exceptional but they bring out the fact that a patient with serious underlying organic heart disease may have multiple attacks of ventricular tachycardia and still carry on relatively normal activity for many years. They also indicate that repeated attacks of ventricular tachycardia may occur in a patient who once had a myocardial infarction, purely as a neurogenic upset without any additional injury to the coronary arteries or the heart muscle. In that sense the attack then behaves as paroxysmal auricular tachycardia does in an otherwise healthy individual.

The duration of the attacks varied from a few seconds to twenty-four days. There were seventeen instances in which the attack lasted one to five hours; eleven, six to twelve hours; nine, twelve to twenty-four hours; eighteen, one

to five days; and fourteen, five to twenty-four days. The longest case on record persisted for seventy-one days while the patient was under observation in the hospital and a probable six additional days prior to admission to the hospital.[25] The patient expired with uncontrolled ventricular tachycardia. The duration of the attack is largely dependent on the promptness with which the diagnosis is made and effective therapy instituted.

The presence of auricular fibrillation during ventricular tachycardia is rather difficult to determine with accuracy. It was assumed to be present if found directly after the ventricular tachycardia disappeared. Accepting this assumption, auricular fibrillation was present in 14 patients of the coronary group. When the ventricular tachycardia was effectively treated with quinidine, the concomitant auricular fibrillation did not generally revert to normal sinus rhythm and even resisted reversion on large doses of quinidine.

The production of ventricular tachycardia by the use of quinidine has been previously reported[8, 26, 27] and was observed in 2 patients in this group. Both had auricular fibrillation and had received large doses of digitalis in an unsuccessful effort to slow the ventricular rate. Quinidine was administered and both patients promptly developed paroxysms of ventricular tachycardia which ceased when the quinidine was discontinued.

Patients with Rheumatic Heart Disease

There were 9 patients (8.4 per cent) in our series who had rheumatic valvular disease. This was present in 15 per cent of the subjects of one reported series[28] and 3 per cent of another.[8] The age of our parents with rheumatic valvular disease ranged from 21 to 62 years; 8 were over 40 years of age. Seven had persistent attacks of tachycardia and 2 intermittent attacks. All the patients with rheumatic valvular disease were in severe congestive failure before the attacks of ventricular tachycardia occurred. One patient was in extremis. Five had coexistent auricular fibrillation. Digitalis had been given to 8 prior to the onset of the tachycardia. In 4 of these 8 the doses were in all likelihood too small to have produced any toxic effects but in the other 4 one might readily suspect that digitalis was in some way responsible for the tachycardia.

Subjects with Normal Hearts

Thirteen patients (12 per cent) had no evidence of organic heart disease. In other reported series, 17 per cent,[5] 14 per cent,[6] and 10 per cent[18] showed no evidence of organic heart disease. The youngest in the present series was 20 years of age and the oldest 53 years. Five had intermittent and 8 persistent attacks. The intermittent attacks were short paroxysms of tachycardia, with the patient usually complaining of palpitation and occasionally of dyspnea. Some of these episodes occurred with great frequency and were so distressing that medical advice was sought. These attacks were precipitated by exercise, emotion, and smoking. In the majority of instances the episodes were of no great significance.

In this group there were 4 patients with persistent tachycardia in whom the clinical features are worthy of comment.

A 20 year old medical student had had recurrent attacks of ventricular tachycardia beginning in his middle teens. All the attacks were related directly to exercise. During eight months of 1945 he had eleven episodes of tachycardia, all of several hours' duration. These either ceased spontaneously or reversion to normal rhythm was effected by the oral administration of quinidine.

A 23 year old dental student had recurrent attacks of palpitation and dyspnea with ventricular tachycardia beginning at the age of 13 years. This patient had from one to nine paroxysms a month, varying in duration from several minutes to thirteen hours. The longest period during which he was free from attacks was two years.

The third patient was a 34 year old woman, whose first attack of ventricular tachycardia lasted twenty days and was refractory to large oral doses of quinidine. Her condition was desperate. Reversion to normal rhythm occurred after a large oral dose of quinidine followed by 1 mg. of atropine. Following this the patient had two more short episodes while receiving prophylactic quinidine, 0.2 Gm. four times a day. She then had no more attacks until nine and ten years later, when she had two episodes. At the present time she is alive and fairly well.

The fourth patient, a 42 year old man, developed auricular fibrillation, paroxysmal ventricular tachycardia, and congestive failure. He had at least

three episodes of ventricular tachycardia during a six weeks' stay in the hospital. Following recovery, he has been working every day; he is symptomless and has no findings suggestive of heart disease at the present time, three years later.

It can be seen that patients without any evidence of organic heart disease may have episodes of ventricular tachycardia and in some cases present the same difficult therapeutic problems and dangers as those with underlying organic heart disease. However, after reversion to normal rhythm the prognosis is excellent.

Miscellaneous Group

Five patients with the Wolff-Parkinson-White syndrome, with peculiar ventricular complexes, have been included in this study. On ordinary inspection the electrocardiographic pattern resembled that of paroxysmal ventricular tachycardia. Three of these cases have previously been reported.[15] The interpretation of the exact mechanism can be disputed. It is well known that the customary disturbances in rhythm associated with the Wolff-Parkinson-White syndrome are auricular in type, usually paroxysmal auricular tachycardia or fibrillation. Therefore, it is quite likely that these 5 cases showing rapid broad ventricular complexes were instances of conduction through the anomalous bundle rather than cases of paroxysmal ventricular tachycardia.[29] The only method of identifying a true ventricular tachycardia, in the presence of the Wolff-Parkinson-White syndrome, would be to detect auricular complexes coming regularly, independently, and more slowly than the ventricular beats. This has not as yet been demonstrated.

Despite the difficulty in interpretation, these five cases are included because they responded in general just as the more classic instances of ventricular tachycardia. None of these patients showed any other evidence of organic heart disease. As a group they were young patients, the ages being 13, 30, 36, 37, and 52 years. Two of these 5 died suddenly, the other 3 remaining quite well. One young boy presented a picture that was confused with and misdiagnosed as an acute myocardial infarction. In one case the tachycardia stopped spontaneously and in another reversion took place after a moderate amount of digitalis was given. However, the role played by digitalis in producing the reversion is doubtful. In the other 3, reversion resulted from quinidine administration. In one case there was a gradual but rapid slowing of the ventricular rate from around 300, before the normal rhythm was established. This is what one might expect from quinidine therapy if the abnormal mechanism was ventricular in origin, for if auricular fibrillation was present it is much more customary to observe an acceleration of the ventricular rate following quinidine, before regularization occurs, than a deceleration.

The important inference to be drawn from these experiences is that although the Wolff-Parkinson-White syndrome with paroxysmal arrhythmias may be unassociated with any other detectable organic heart disease, sudden death is not a very rare eventuality.

The last patient in this group was a young man, 30 years of age, who had Eisemenger's complex. The diagnosis was confirmed by intracardiac catheterization studies. His primary complaints were palpitation and attacks of syncope. When the spells of unconsciousness became frequent, he had to discontinue his work which otherwise he would have been able to perform. It was found that his difficulty was due to ventricular extrasystoles, which occasionally developed into short runs of paroxysmal ventricular tachycardia and were followed by syncopal attacks. He seemed to be helped by a bilateral upper dorsal sympathectomy and quinidine therapy.

Part Played by Digitalis

Forty-seven patients received digitalis in varying amounts prior to the onset of ventricular tachycardia. Twenty-six were on what was considered maintenance doses or less at the time the tachycardia developed. In these patients it was doubtful if digitalis played any part in the precipitation of the episodes. Thirteen received what was considered as probably excessive doses. In these digitalis may have been important in the production of the paroxysms. In 6 there was definite evidence of digitalis intoxication, such as nausea, vomiting, premature ventricular contractions, and bigem-

inal and trigeminal rhythm. In these cases digitalis may have precipitated the arrhythmia but conclusive evidence of this is not available. Two patients with definite digitalis intoxication had bidirectional ventricular tachycardia and one with probable intoxication had alternation of the ventricular complexes.

Digitalis has long been considered as one of the more common precipitating factors in the development of ventricular tachycardia. Lundy and McLellan[6] in their review in 1934 stated that digitalis was responsible for 100 per cent of the cases in which alternating bidirectional complexes were observed. Marvin[30] reported 5 cases of ventricular tachycardia with alternation of the complexes and postulated that factors other than digitalis alone must play a part as 3 patients had no headache, nausea, or vomiting and only one had yellow vision. Scherf and Kisch[31] in a study of 18 patients showing bidirectional ventricular tachycardia found that all but 4 were receiving digitalis at the time the tachycardia developed. They also noted that there was no definite relationship between the amount of digitalis and the development of ventricular tachycardia. They believed that there must be in addition to the digitalis factor an injured myocardium.

Digitalis cannot be looked upon as an important or frequent cause of ventricular tachycardia when it is appreciated that in this very clinic from which the cases are being analyzed, thousands of different individuals have received full doses of digitalis and yet only a very few have ever showed this arrhythmia. In one patient with valvular heart disease who had had previous attacks of paroxysmal ventricular tachycardia an attack appeared for the first time directly after a full dose of digitalis had been given. There was little doubt about the relationship between cause and effect in this instance. In another patient it was clearly established that the ventricular rate during the ventricular tachycardia accelerated under digitalis therapy. It is therefore very difficult to evaluate, with any degree of exactness, what part digitalis had in evoking the attacks of tachycardia, though we are of the opinion that it does play a role in a small number of cases.

Clinical Features

The clinical features that characterize the episodes of ventricular tachycardia have been studied in seventy-seven attacks in which adequate data were available. The onset of paroxysmal ventricular tachycardia may be entirely unnoticed by the patients. In such cases the diagnosis is made only when the examining physician or nurse notices that the patient has a rapid heart rate, and the physician investigates the rapid rhythm more thoroughly. There are, however, certain clinical features that make one suspect that the patient is having a bout of paroxysmal rapid heart action. The sudden onset of palpitation and slight to moderate dyspnea were the most common subjective symptoms noticed by the patients in this study. Dizziness and syncopal attacks with loss of consciousness may usher in the episodes. These symptoms may occur regardless of whether or not organic heart disease is present. Cerebral manifestations such as these were present in 13 patients and have been described previously as occurring in association with paroxysmal tachycardia.[32] There is another type of syncope that may occur, for some patients with complete heart block may have a short paroxysm of ventricular tachycardia or fibrillation which is then followed by ventricular arrest of sufficient length to cause unconsciousness and convulsions. Such a mechanism producing Adams-Stokes episodes in persons with complete heart block is well known.[26, 33–35] There were 5 patients in this series who exhibited these findings. One patient, a 46 year old woman, had had complete heart block with Adam-Stokes attacks for a period of three years, the latter always being preceded by paroxysms of ventricular tachycardia or ventricular fibrillation. The patient failed to respond to any type of therapy and finally expired suddenly during an episode. At postmortem examination the heart weighed 360 grams, there was no evidence of coronary atherosclerosis, the interventricular septum showed no abnormalities, nor were there

any other structural abnormalities of the heart. Therefore, judged by postmortem examination, this patient had a normal heart.

Eighteen patients noticed substernal and precordial pain with the onset of the attack of tachycardia. The pain may be identical with that of angina pectoris[23] or of an acute myocardial infarction. In patients who have had previous episodes of angina pectoris or a previous myocardial infarction the pain was usually not as severe as that due to the angina or infarction. The majority of patients described the pain as a dull ache, a heavy feeling, or a choking sensation.

In any patient, especially in one with an acute myocardial infarction, in whom sudden collapse occurs, ventricular tachycardia should be suspected. With the onset of the rapid rate there may be a marked fall in blood pressure; the skin becomes cold and clammy and profuse sweating occurs. The condition changes in a matter of minutes from satisfactory to critical. There were 44 patients in shock during the episode of ventricular tachycardia. The shock varied from mild, in which the systolic blood pressure was slightly less than 100 mm., to profound in which the blood pressure was unobtainable. In sixty-two instances congestive heart failure was present. The congestive failure was manifested by moist râles at the lung bases or throughout the chest and varying degrees of right-sided failure. These variations depended on the type of underlying heart disease and the duration of the rapid rate.

It may be said in summary that a patient with ventricular tachycardia may be asymptomatic during the attack or may have syncopal episodes, dizziness, or sudden collapse with the onset or during the paroxysm. Chest pain similar in all respects to that of angina pectoris may occur.

Prognosis

Strauss[5] reported that in 50 patients with ventricular tachycardia with underlying organic heart disease, 40 were dead within three hours to six months of the onset, with an average duration of life of twenty-four days. Cooke and White[7] noted that 17 of 21 patients with coronary artery disease expired in from a few hours to eighteen months. Follow-up information was available on 84 patients in this group of 107. In 42 patients in whom ventricular tachycardia complicated an acute myocardial infarction, 28, or 64 per cent, were dead within one month after the attack of tachycardia. Ten lived two years or longer; the longest period of survival was eleven years. Of 24 patients with coronary sclerosis and attacks of ventricular tachycardia, 10 were dead within six months after the first attack. The remainder lived for periods varying from one to ten years. The outlook, as can be seen, is particularly grave in those in whom the tachycardia complicates an acute myocardial infarction. Patients, however, may live for many years if there is recovery from the acute attack, and in addition these years may be useful and productive ones.

There was follow-up information available on 6 patients with rheumatic valvular disease and ventricular tachycardia. Three were dead within one month after the episode. Two died within eighteen months and one is alive at the end of five years.

The patients with no underlying heart disease have a very favorable prognosis as has been previously mentioned.[5] There were 13 such patients in this group. In one patient, death was due to Adams-Stokes attacks which had recurred for three years; in another it was due to a neoplasm. Eight were alive and well for periods of from nine to twenty-one years after the attacks. In some of the patients the paroxysms ceased spontaneously. The prognosis in these patients was not affected by their having multiple attacks.

In general it may be said that although paroxysmal ventricular tachycardia is a serious complication of coronary artery disease, there are enough instances in which a satisfactory and useful recovery takes place to make one hopeful. It appears to be an especially ominous complication when occurring in association with rheumatic valvular heart disease but the outlook may be very favorable when the arrhythmia is unassociated with any structural disease of the heart.

Treatment

Several drugs have been used in the treatment of this arrhythmia. In 1921, Scott[11] successfully used quinidine orally to control recurrent episodes of ventricular tachycardia. In 1927, Levine and Stevens[12] tried intravenous quinidine therapy in an effort to effect reversion of ventricular tachycardia complicating an acute myocardial infarction. This attempt was unsuccessful with the small intravenous dose used but the arrhythmia was reverted to normal sinus rhythm with much larger oral doses of quinidine. In 1937, Hepburn and Rykert[27] successfully treated 8 patients having paroxysmal ventricular tachycardia with quinidine administered intravenously. These authors advocated the use of quinidine intravenously only in patients who were moribund or in shock.

Zwillinger[36] first reported the value of magnesium sulfate in patients with ventricular tachycardia. Boyd and Scherf[37] treated 2 patients with this drug; the treatment was effective in one. In 1932, Sampson and Anderson[38] used potassium salts in an effort to control auricular and ventricular ectopic beats and auricular and ventricular tachycardia. One patient with ventricular tachycardia was treated successfully but in another a paradoxical effect occurred and ventricular tachycardia was produced. Stempien and Katz[39] used potassium chloride with success in a case that was refractory to all other forms of therapy. Salley[14] described the use of atropine with quinidine after the ventricular rate has been slowed by the latter. Sabathie[40] noted that morphine given intravenously was of value in 9 of 10 patients.

In some instances, both the persistent form (of hours' or days' duration) of the tachycardia and the intermittent type ceased spontaneously without any form of therapy. There were 6 patients with persistent tachycardia in whom reversion was effected without treatment and 12 with intermittent episodes who required no therapy. There were 4 patients who expired before any type of treatment could be given.

Fifty-seven episodes of ventricular tachycardia of the persistent type were treated with oral quinidine. Forty-six responded favorably (fig. 4). The dosage varied from 0.2 Gm. to 2.5 Gm. in a single dose and the total dosage at the time of reversion was from 0.2 Gm. to 45.8 grams. There were eleven failures. Of these eleven, in five episodes reversion to normal rhythm was brought about by intravenous quinidine therapy, in three the reversion was spontaneous, in one response was obtained following rectal administration of the drug, and in two reversion was not effected and the patient expired subsequently. Quinidine was not a factor in the fatalities.

TABLE 2.—*Reversion with Oral Quinidine in Persistent Paroxysmal Ventricular Tachycardia*

Maximum Single Successful Dose in Grams	No. of Episodes Reverting	Total Amount before Reversion in Grams
0.2	6	0.2–1.6
0.3	6	0.3–0.9
0.4	4	0.4–1.0
0.6	8	0.6–2.4
0.7	4	2.2–2.5
0.8	9	0.8–6.5
1.0	3	2.1–4.3
1.2	2	1.8–3.7
1.4	1	5.6
1.5	2	7.2–8.0
2.5	1	45.8

The time of reversion following the last oral dose of quinidine was accurately noted in thirty-four episodes, the shortest time being twenty-five minutes and the longest four hours. The usual time was two to four hours. The usual method of the oral administration of quinidine was to start the patient on 0.2 Gm. and increase the dosage 0.2 Gm. each four hours until reversion took place. The first dose also served as an indicator of any sensitivity to the drug. In several patients requiring intravenous quinidine therapy, the dose necessary to produce reversion was less than the largest previous oral dose which had been inadequate.

Ten patients with intermittent episodes of ventricular tachycardia were given quinidine orally. The amount used was 0.2 to 0.6 Gm. three times a day. Under these conditions, the episodes in 6 patients were completely controlled and in 3 the treatment was of doubtful value.

In thirty-one persistent episodes of ventricular tachycardia, quinidine was administered intravenously. The treatment was successful in 20 cases. The single intravenous doses varied from 0.2 to 1.5 grams. In six of the twenty episodes, reversion was not effected on the first intravenous dose but was accomplished on the second. The second intravenous dose varied greatly in amount. There were eleven failures with this method. In 2 of these 11 patients, reversion to normal sinus rhythm followed a larger single oral dose of quinidine, in one it followed the administration of magnesium sulfate, in one, failure followed three injections of quinidine in fifteen hours (total 3.4 Gm.) and reversion took place spontaneously the next day. In one patient the therapy was stopped after 0.3 Gm., in 2 patients death was the result of ventricular tachycardia, and in 4 death was due to quinidine toxicity. The first of the four fatalities due to quinidine occurred in a 55 year old woman, with mitral stenosis and mitral insufficiency, who was in a moribund state with pulmonary edema and shock. She died after 0.6 Gm. quinidine been given in 100 cc. of 5.0 per cent glucose solution in twenty minutes. The second patient was a man, 63 years of age, with hypertension, aortic stenosis, aortic insufficiency, and an acute myocardial infarction. He was in uremic coma and had congestive heart failure. He was given 0.3 Gm. quinidine in a few minutes, when respirations suddenly ceased. The third, a woman, 58 years old, with an acute myocardial infarction, in extreme shock, was given 0.6 Gm. quinidine in 200 cc. of solution in twenty-five minutes. The heart rate fell from 137 to 100 beats per minute. She then received 0.6 Gm. quinidine in one to two minutes and respirations ceased two minutes later. The fourth, a woman 51 years old, with mitral stenosis, mitral insufficiency, auricular fibrillation, and marked congestive failure, was in extremis with a blood pressure of 80/60. After 0.1 Gm. quinidine in 30 cc. of solution had been given slowly, she expired. It is clear from these 4 cases that all fatalities occurred in patients who were in extremis. In each instance it did not appear that they would have survived for many minutes or more than a few hours.

Thirteen patients were treated with magnesium sulfate given intravenously in doses varying from 2 to 5 grams. One patient received only 1 gram. Nine received two or more injections, usually within thirty minutes of each other. In 2 cases, reversion to normal sinus rhythm took place and in one case the ventricular tachycardia was converted to 2:1 flutter. The side effects noted were similar to those described by Boyd and Scherf,[37] namely, a feeling of intense heat, flushing, and nausea. The value of magnesium sulfate is not great but the drug is relatively safe and therefore can be tried early. It proved effective rarely when quinidine failed.

In 7 patients, atropine sulfate was given either intravenously or intramuscularly in doses of 1 or 2 milligrams. The atropine was usually given after maximum slowing of the ventricular rate had been brought about by quinidine. The most dramatic effect occurred in the patient previously described by Salley,[14] in whom the ventricular rate was slowed from 160 to 112 following 2.0 Gm. quinidine given by mouth; then 2 mg. of atropine were given intramuscularly and almost immediately complete heart block with a ventricular rate of 30 developed. There were 2 other patients in whom atropine may have been instrumental in causing reversion of the tachycardia to normal sinus rhythm. One patient had had ventricular tachycardia for twenty-one days and had failed to respond to magnesium sulfate, quinidine either orally or intravenously, and potassium salts. Finally 1 Gm. of quinidine was given intravenously and the rate fell from 180 to 110; 2 mg. of atropine were given and normal sinus rhythm occurred almost at once. The second patient had had ventricular tachycardia for twenty days and had not responded to any form of therapy. She was given 2.5 Gm. of quinidine by mouth in a single dose. After the heart rate slowed, 1 mg. of atropine was given and reversion took place in about two hours. The atropine may not have played any part in the reversion in this case. In the remaining cases atropine was of no value. Salley[14] suggested that atropine breaks up the circus of ventricular tachycardia by paralyzing the vagus and that this effect lengthens the refractory period of the ven-

tricles. Wilburne and collaborators[41] produced ventricular tachycardia in animals by the intravenous injection of epinephrine and found that the arrhythmia could be prevented by the use of atropine prior to the administration of epinephrine.

Potassium salts were used only in 2 patients and proved to be of no value. Morphine (30 mg.) was given intravenously to one patient and failed to cause reversion.

The drug of choice in the treatment of ventricular tachycardia, in our opinion, is quinidine. The route of administration of the quinidine depends on the clinical condition of the patient. If the condition is critical, the drug should be given by the intravenous route. This is a matter of individual judgement and difficult to express in very definitive terms. In general, if it appears that the patient is likely to succumb in minutes or hours the intravenous route is preferable, whereas if he is likely to survive for days the oral method might be employed. Quinidine hydrochloride, diluted (0.6 Gm. with 200 cc. of 5 per cent glucose in distilled water), may be given by slow drip over a period of about one hour.* Electrocardiograms, made continuously or frequently during the injection, are helpful in that the procedure can be stopped instantly if reversion takes place or if any threatening disturbance in the cardiac mechanism occurs. If the first intravenous injection fails, a similar or larger amount may be given within several hours.

There are many difficulties in appraising and predicting the effect of oral quinidine dosage. One common error in general practice is to continue the same oral dosage day after day. This applies not only to the treatment of paroxysmal ventricular tachycardia but to auricular fibrillation and other arrhythmias. If a certain program, such as 0.2 to 0.3 Gm. three times a day, is not effective in a day or two it is not likely to be any more effective if continued indefinitely.[42] The maximum effective blood level of the drug is reached about an hour or two after oral administration and there is practically none left in the blood stream twenty-four hours later.[43, 44] On the other hand, the blood level need not be the determining factor in causing an effect on the heart or reversion to normal sinus rhythm. This is well illustrated by the experiences we have had in which auricular fibrillation has reverted to normal rhythm six hours or more after the last dose had been given. In such cases the blood level must have passed its peak when sudden regularization took place.

In general it is of little importance to estimate the total amount of the drug employed. The significant factor is the largest single dose that is required to effect reversion. Many patients have had 10 or 20 Gm. of quinidine given as a total dose over many days without any beneficial effect on their arrhythmia, while a total of 1 or 2 Gm. when given in increasing doses over the course of one or two days was effective. In administering quinidine either orally or intravenously it is helpful to observe a slowing of the ventricle which occurs quite frequently. This indicates a partial effect in the right direction and makes one think that further dosage might produce the desired regularization.

Another value of quinidine is that even if the drug does not cause reversion of the ventricular tachycardia, it may keep the ventricular rate at a slower rate and improve the general state of the patient.[45] Such an effect has been noted in many of the patients in this series. Quinidine has also been reported as being valuable in controlling bidirectional ventricular tachycardia.[46]

Much has been said and written about the toxic effects of quinidine. In the treatment of ventricular tachycardia these matters are of very little importance as the condition under consideration is already critical and often fatal if uncontrolled. Excessive quinidine may produce shock but these patients are not infrequently already in shock. In many cases marked distortion of the electrocardiograms resulted from the large doses of quinidine. Had such abnormalities been used as a criterion for cessation of therapy the attacks would not have been controlled. It is difficult to define the exact indication for discontinuing the drug. It is reasonable to regard sudden syncope or some other obviously desperate untoward complication such as convulsions

*Quinidine hydrochloride supplied through the courtesy of Brewer & Company, Worcester, Mass.

as sufficient reason to discontinue the treatment. The fact that the patient becomes nauseated, dizzy, weak, or develops diarrhea or ringing of the ears should not discourage the physician from persisting with this therapy, when the alternative is likely to be a fatal termination.

Summary

1. The following observations were made from a study of 107 patients with paroxysmal ventricular tachycardia, varying in age from 13 to 83 years, with the majority between 50 and 70 years.

2. The diagnosis can often be suspected by simple bedside examination but is better confirmed by electrocardiographic studies. On clinical examination an occasional case can be overlooked because only one heart sound may be present to each cardiac cycle so that the physician estimates the rate at one-half its actual value.

3. In 79 patients (74 per cent) the underlying cause of the heart disease was coronary artery disease, generally with recent or old myocardial infarction. Nine patients had rheumatic heart disease, 13 no heart disease, and 6 miscellaneous conditions.

4. There were 27 patients who had recurrences of prolonged attacks over the course of months or years.

5. The duration of the prolonged attacks varied from hours to twenty-four days.

6. It seemed that digitalis played a role in the precipitation of the paroxysmal ventricular tachycardia in only a small number of instances.

7. Although the attack of tachycardia may be symptomless, it is frequently accompanied by substernal pain, sudden collapse, shock, dyspnea, or syncope.

8. The immediate prognosis of the attack of tachycardia is very good, since in all but a few subjects normal rhythm was resumed following appropriate therapy. The ultimate prognosis is grave in those who have underlying coronary or valvular disease; however, a fair number of these were able to carry on a useful occupation for years.

9. In the group of subjects with no organic heart disease the prognosis is generally excellent. Even in this group the threat of sudden death is present; death during a paroxysm occurred in one patient who had a structurally normal heart post mortem.

10. In this study, magnesium sulfate administered intravenously was occasionally of value, potassium salts given orally were of no value in the few instances in which they were employed, and morphine given intravenously failed on the one occasion it was tried. The treatment of choice was quinidine therapy. The oral administration was successful in forty-six of fifty-seven episodes. The intravenous route, used in the more desperate cases, was successful in twenty out of thirty-one attacks.

11. The intelligent use of quinidine was found to be of great value in this condition and not infrequently life saving.

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Coarctation of the Aorta

Surgical Treatment of One Hundred Cases

By ROBERT E. GROSS, M.D.

Coarctation of the aorta can be recognized in most instances by simple findings of physical examination. The anomaly is one which carries a variable prognosis. The condition may be tolerated through a long life with little incapacitation or may be accompanied by early and serious complications in the form of cardiac failure, aortic rupture, or intracranial hemorrhage. In a high percentage of patients it is possible to remove the aortic block and establish a pathway of satisfactory size. A series of cases shows that there is an excellent chance of relieving hypertension by such surgery. Mortality rates for these operations have not been unduly high. Certain complicated types of cases carry too high a risk and should not be accepted for surgery.

COARCTATION of the aorta has been the subject of numerous contributions to the literature by various authors and no attempt will be made here to give detailed descriptions of the clinical picture or to discuss the intricacies of surgical problems which are encountered in the treatment of this condition. Instead, attention will be focused upon the prognosis, the recognition of the condition, and upon the risks and results of surgical therapy. These notes are based upon a series of 100 patients who have been operated upon by the author for an aortic obstruction.

There has long been a tendency to regard coarctation of the aorta as having two somewhat distinct forms. The "infantile type" supposedly included a group in which there was a very long segment of constriction, usually involving the distal third or half of the aortic arch, often associated with severe intracardiac abnormality, and commonly leading to death within the first year or two of life; because of this last distinction the term "infantile" was affixed. In contrast, the "adult type" was supposed to have a blockage of only a short segment, was prone to involve the aorta beyond the origin of the left subclavian artery, and presumably was not accompanied by important intracardiac malformations; the prognosis was such that a large number of these subjects lived to adult years. There is little point in classifying coarctations of the aorta into these two artificial groups, because a good deal of overlapping tends to make such a classification arbitrary and useless. It is becoming clear that a short aortic obstruction alone can lead to cardiac decompensation or even fatality in the early months of life. Conversely, a considerable number of long aortic strictures are found in adults who also have serious intracardiac congenital anomalies. Such experiences emphasize the desirability of abandoning the separation into "infantile" and "adult" forms.

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PROGNOSIS

The fact that a few human subjects with aortic narrowing have lived to advanced old age has given a false impression to many physicians that the prognosis is generally not serious. There is now increasing evidence to show that coarctation leads to crippling complications or even fatality in a very large percentage of cases.

It is not possible to obtain satisfactory estimates of the prognosis by reviewing case reports from the literature, because there has been a widespread tendency to record those deaths which were caused by the aortic abnormality and to leave unpublished those wherein exitus occurred from some unrelated disease. A summary drawn from the existing reports would tend to show a prognosis which is more grave than is actually true. In an effort to determine the outlook for patients with this malformation, Reifenstein, Levine, and Gross[17] reviewed postmortem material from large hospitals of

the Greater-Boston area and studied all cases of coarctation of the aorta, whether or not the abnormality had contributed to the death. The review included those patients who had died of coarctation of the aorta or one of its complications and it likewise listed those who had succumbed to unrelated diseases and in whom the coarctation was an incidental clinical or pathologic finding. In this way it was hoped that a cross-sampling of the community could be obtained and that it would be possible to determine what was happening to people with coarctation of the aorta. From this survey certain general statements can be made which give a fair idea of the prognosis. The subjects could be placed in one of four groups, each comprising approximately one-quarter of the entire series:

1. About one-fourth (26 per cent) of the patients lived far into adult life—some to old age—with very little or no incapacitation. In this group, deaths were most common in the fifth decade of life, the average age at death being 47 years. Some of these patients had mild or moderate symptoms for which they had sought medical advice or help; the remainder had a lesion the presence of which was totally unsuspected until the time of autopsy. Taken as a whole, these patients had few difficulties and they enjoyed long and useful lives.

2. Approximately one-fourth (22 per cent) of the subjects died from bacterial endocarditis or aortitis, the causative organism of which was usually the *Streptococcus viridans*. Deaths from bacterial endocarditis or aortitis occurred throughout the first five decades of life, but they were most common in the third decade; the average age at death was 28 years. By the time death occurred the widespread distribution of the vegetations often made it difficult or impossible to determine whether the coarctation or some coexisting cardiovascular abnormality was the focus on which the bacterial invasion had originally started. There were a few septal defects, several examples of rheumatic valvular disease, and many congenitally deformed valves, which makes one wonder whether the coarctation or the associated lesion was more responsible for promoting development of the superimposed infection. Our studies would seem to indicate that about 40 per cent of all patients with coarctation of the aorta have a bicuspid aortic valve, though this figure is somewhat higher than is reported in other series. This emphasizes the fact that bacterial endocarditis is not necessarily a complication of coarctation itself, but that there are frequent opportunities for it to start on an associated cardiovascular defect. Suffice it to say that *Streptococcus viridans* infections have been a real threat to those who possess an aortic obstruction; probably this hazard is greatly minimized today when the newer chemotherapeutic agents are available.

3. In about one-fourth (23 per cent) of the cases there was sudden death from rupture of the aorta. Such catastrophes usually occurred in the second or third decades of life, with an average at 27 years. The aorta was most apt to rupture when there was pre-existing hypertension, but fatal hemorrhage has been known to take place when the arterial pressures were relatively normal. Rupture rarely occurred just proximal to the coarctation. In about four-fifths of the subjects it appeared in the ascending aortic arch, while in about one-fifth it occurred in the thinned-out aorta just beyond the block or in one of the dilated intercostal arteries which joined the lower aortic segment.

4. A little more than one-fourth (29 per cent) of the subjects died because of the hypertensive state. Deaths from cardiac failure were about twice as numerous as those from intracranial hemorrhage. Fatalities from congestive failure were most common in the fourth and fifth decades, the average age at death being 39 years. Deaths from intracranial hemorrhage had peak incidences in the second and third decades, with an average at 28 years. As has been pointed out before, pathologic studies often show that subjects with coarctation of the aorta also have congenital aneurysms of vessels at the base of the brain; hence the appearance of intracranial bleeding should not always be ascribed to hypertension alone. However, it is fair to assume that a congenital aneurysm of the brain is more apt to rupture when it is subjected to high arterial tensions.

As one summarizes material from all of the above four groups, several general statements

can be made. The average age at death (including the patients who died from incidental causes) was about 35 years. In those who died from coarctation or one of its complications, the average age at death was about 30 years. The seriousness of the prognosis can be indicated by pointing out that the general population is in excellent health between the ages of 10 and 30 years and deaths during this period are at a low ebb; in contrast, about 40 per cent of all human beings with coarctation die between the ages of 10 and 30 years. Sixty per cent of all coarctation patients apparently die by the fortieth year. It has become quite clear that, while some human beings may live a long and useful life with coarctation, the abnormality is one which brings great hazards to its possessor. It is this knowledge which prompts surgeons to attempt removal of aortic obstructions in the hope of bettering the outlook, particularly in alleviation of the hypertensive state.

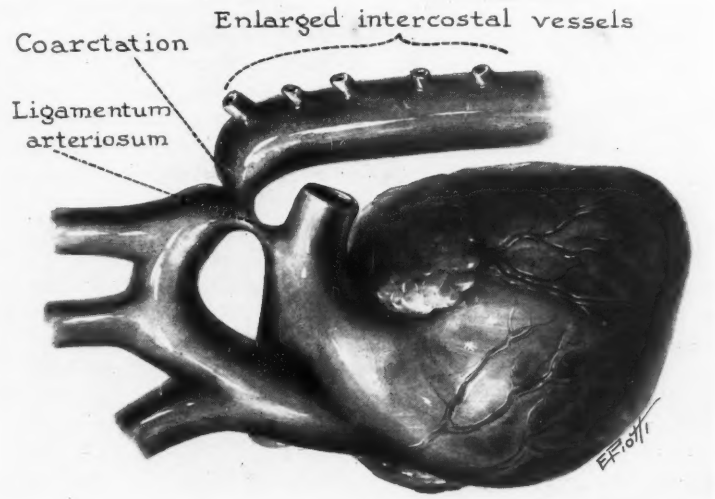

FIG. 1.—Drawing showing typical pathologic findings in a case of coarctation of the aorta. The first portion of the descending aorta is constricted. At the point of coarctation the aorta is kinked and angulated toward the pulmonary artery because of the pull exerted by the ligamentum arteriosum.

RECOGNITION OF COARCTATION OF THE AORTA

Figure 1 depicts the typical pathologic findings in a case of coarctation of the aorta.

With but rare exceptions, coarctation of the aorta can be recognized quickly and with great accuracy by finding a few signs which are evident by physical examination. In these days, when there is an increasing tendency to employ expensive and complicated laboratory tests, it is appropriate to point out that coarctation can be accurately diagnosed—or certainly suspected—in a few moments by the intelligent use of one's finger tips, a stethoscope, and a sphygmomanometer.

Of greatest importance in detecting an aortic block is the disparity of blood pressures in the arms and legs. Normally, the systolic level in the legs is 20 to 40 mm. of mercury higher than that in the arms; in the presence of an aortic block the leg pressures are far below those of the arms. Pulsations in the legs or lower part of the body are diminished or absent. If femoral pulsations appear to be reduced in intensity, the actual pressures in the popliteal artery should be checked with a sphygmomanometer. Under normal circumstances the beats in the femoral and radial arteries come at essentially the same instant, but in the presence of a coarctation the femoral artery impulse starts

at a somewhat later time and there is a very slow rise in the femoral pulse wave. This phenomenon was noted as early as 1870 by Scheele. Accurate tracings on the delayed onset of the femoral pulse and the slow rise thereof were made by Laubry and Marre in 1916, by Railsbach and Dock[16] in 1929, and by Blumgart, Lawrence, and Ernstene[4] in 1931. Sir Thomas Lewis[15] commented at length upon these observations and pointed out that the slight delay in the onset of femoral beat is probably not detectable by ordinary methods of palpation but that the slow rise of the femoral wave makes its summit come at a time which is distinctly later (as much as 0.145 second) than the radial one. This difference in timing can be recognized easily by simultaneous palpation of the radial and femoral arteries.

In young subjects with coarctation the pressures in an arm may be normal or only slightly elevated, whereas in older persons one commonly finds a hypertension of moderate or marked degree. Certainly, in the majority of patients beyond the first decade, hypertension has become firmly established. The systolic level may be greatly elevated; the diastolic pressure can be raised to 80, 90, or 100 mm. Hg or even higher in advanced cases.

Arterial pressures should be measured in both arms because this might give a clue regarding the position of high aortic constrictions. Differences of 10, 20, or even 30 mm. Hg between the two arms can be found, even if the obstruction is beyond the origin of the left subclavian artery. Conversely, differences greater than 30 or 40 mm. Hg suggest that the aorta is narrowed in a place proximal to the origin of the left subclavian artery; a point of great significance when discussing the feasibility of surgery. It is well to bear in mind that large differences in arm pressures can also be caused by an atresia of the first part of the left subclavian artery, an observation in two of our patients. Stephens described a rare finding in which the right subclavian artery did not originate from the innominate artery, but instead arose from the aorta below the obstruction; the arterial pressure in the right arm was distinctly lower than that in the left.

Blood pressure determinations made during an office visit or when a patient is at rest in bed do not necessarily indicate the state of affairs which exist when the subject is undergoing exercise or the physical strain of daily life. The value observed during rest may be distinctly lower than that which actually exists during routine activity. It is generally known that a normal person reacts to exercise by slight or moderate elevation in the blood pressure, but it is seldom appreciated that a patient with coarctation often responds by extraordinary rises. In the latter, the increased demands of the body raise the cardiac output but the large quantity of blood cannot pass through an obstructed vascular bed; hence there is a momentary and steep upswing in pressure throughout the upper part of the body.

Collateral arterial circulation is by no means constantly observed, but when it is found it strongly favors the diagnosis of coarctation. It is rarely seen in children, but beyond the first decade it becomes noticeable, particularly in thin subjects wherein the vessels can be more easily detected by palpation and inspection. Pulsations may be seen and felt above and below the clavicles, in the axillae, along the intercostal spaces in the forward half of the chest, in the epigastrium, and particularly over the back. When the establishment of collateral circulation is marked, pulsations may appear in the anterior abdominal wall and at times can be traced downward to the inguinal regions.

There is nothing characteristic about the murmurs which are found. The most important thing to say about them is that they are extremely variable in character, in intensity, and in location. Most often, but by no means constantly, there is a systolic murmur of mild or moderate intensity over the precordium—especially toward the base—which is transmitted with slight diminution to the left side of the interscapular area. In rare instances it may be louder in the back than it is in the front of the chest. Murmurs over the back do not, by their point of maximum loudness, give any indication of the actual level of the aortic anomaly. A few subjects with coarctation have absolutely no murmur; a small number have continuous ones.

As yet we have little in the way of accurate

information regarding the sources of murmurs which appear in patients with coarctation. It is tempting to think that blood rushing through a narrowed aortic segment sets up the vibration but there is ample proof that this is not always true. While the systolic sound in some instances is known to come from this area, in other cases it almost certainly originates from an angulated collateral channel, an associated septal defect, or a bicuspid aortic valve.

Particular attention must be paid to a diastolic murmur. If it is continuous with the systolic element, and is loudest in the pulmonary area, it may suggest the presence of a patent ductus arteriosus; if such a continuous murmur is most prominent over the back it may be indicative of blood rushing through large and tortuous collateral arteries. Conversely, if the diastolic murmur is heard in the aortic area or to the left of the sternum, and especially if it has a to-and-fro quality in relation to the systolic component, one should strongly suspect aortic valve regurgitation. Slight regurgitations may not be accompanied by any depression in the diastolic level of blood pressure, but marked regurgitation is accompanied by a definite lowering.

Electrocardiographic tracings are an important part of the examination, not because of help in recognition of coarctation, but because of the evidence that they might give regarding myocardial damage or cardiac insufficiency. These studies are of the highest importance when attempting to determine whether a given patient will stand surgical correction of an aortic obstruction.

While there is little need to comment on the picture of cardiac failure in adults which can follow long-standing hypertension, it might be well to call attention to a small group of babies who apparently have cardiac embarrassment because of an aortic block. Presumably, these youngsters remain in fair health as long as the ductus arteriosus stays patent and blood can flow back from the engorged upper portion of aorta into the pulmonary bed. When the ductus closes and this relief mechanism is lost, the left ventricle must pump into a peripheral vascular system which has a high degree of obstruction and which has not yet developed many collateral channels. I have seen eight babies within the first year of life who had marked cardiac enlargement, dyspnea, cough, enlarged liver, and other signs of a failing heart. This decompensation was secondary to hypertension from an aortic block, the presence of which could be easily detected by physical signs. Two of these infants died from cardiac failure but the others could be tided over (by hospitalization, oxygen therapy, digitalization, and other measures) until they regained cardiac compensation. During this precarious interval they probably developed collateral pathways which allowed an easier outflow of blood and which permitted the heart to regain some stability.

By roentgenographic study there may be certain findings in childhood to help support the diagnosis of coarctation, but in adult years the changes usually become more pronounced and clearly indicate the presence of this abnormality. In infancy one seldom finds more than generalized cardiac enlargement, unless there happens to be additional evidence of circulatory failure. During the first eight or ten years of life there may be little variation from the normal except possibly for some left ventricular enlargement and diminution in the size of the aortic knob. Beyond the teens the roentgenologic findings are more numerous and more conclusive. The heart is apt to show mild or moderate increase in size, particularly of the left ventricle. Great enlargements should arouse suspicion regarding the possibility of some other abnormality, myocarditis, coexisting rheumatic endocardial disease, or even cardiac failure. The base of the ascending arch is apt to be widened. The aortic knob or the distal part of the aortic arch lacks its normal prominence. This is a feature of considerable importance, particularly when it is associated with a widened ascending arch; it is in distinct contrast to the picture in essential hypertension wherein the entire arch is dilated, tortuous, prominent, and clearly defined. Though it is by no means a constant finding, the shadow of the descending aorta seems indented if the patient can be turned to an angle which will separate it from the spine. With a swallow of barium in the esophagus, some compression is usually

found on its left side, near the level of the coarctation; this esophageal deformity can come from pressure by the aorta which is dilated just beyond the obstruction or it can be made by enlarged, right, intercostal arteries which cross the mediastinum to enter the distal aorta. Scalloping of the inferior edges of the posterolateral portions of ribs is pathognomonic of an aortic block with compensatory collateral circulation. Such notching is seldom found in the upper and lower two or three ribs. Of rare occurrence, but of particular interest, is the case described by Bing and his associates[2] in which the left subclavian artery arose from the aorta below its block; there were few collateral channels on the left side of the chest and the rib notchings were confined to the right side. We have seen a similar situation in a 12 year old girl in whom the first portion of the left subclavian artery was atretic; chest films showed rib notches which were distinctly more marked on the right than on the left. In this same category is the case of Stephens in which the right subclavian artery arose from the aorta below the obstruction, so that the rib notches were found only on the left side of the chest.

Though exceedingly rare, coarctation may appear in the lower portion of the thorax, or even in the abdominal aorta. Under these circumstances it is evident that the aortic knob would be normal in appearance but that the collateral channels should be over the abdomen and lower chest; rib notches would probably appear only on the lowermost ribs.

Further information regarding the exact position, the length of the stricture, and allied data, is obtainable by angiocardiographic means. The dye can be injected either by the intravenous route or in a retro-arterial manner. Seventy per cent Diodrast, if injected quickly into a vein, will usually remain in sufficient concentration through the circulation so that the aortic arch and its branches can be seen in serial films. Another technic is that in which visualization is obtained by introducing a polyethylene catheter into the left axillary artery, threading it back through the left subclavian artery into the aorta, at which time the injection is made. Freeman and more recently Burford and Carson[7] have exhibited excellent pictures of the great vessels by injecting Diodrast down one of the neck arteries, preferably the left common carotid. On several occasions I have been misled by angiocardiography. At times the dye would show the upper end of the narrowed area but did not give information regarding the length of the stricture. In other cases, where there was a complete aortic block, nothing was learned about the segment of aorta below it. Presumably, angiocardiography should be of assistance in deciding which cases are suitable for surgery and which are not, but I have had disappointments in this regard. This was especially true in older patients when visualization showed an arrangement of vessels which suggested that removal of the constricted area would be feasible; when the chest was opened the vessels were found to be rigid and surgical attack had to be abandoned. Angiocardiography is not an essential part of a routine work-up, but it can be of value in those cases where some special interest is aroused by unusual or inexplicable findings.

The diagnosis of coarctation of the aorta can apparently be made from ballistocardiographic tracings; there is a shortening of the J-K stroke. While this phenomenon is an interesting observation, such investigation can hardly be classed as a method of practical, routine study.

Surgical Attack on the Problem

There are four general ways in which surgery might offer some relief for the hypertension of coarctation. These include sympathectomy, excision of the coarctation and anastomosis of the left subclavian artery to the distal aorta, removal of the coarctation and end-to-end reconstruction of the aorta, and excision of the coarctation followed by the insertion of a graft to bridge the resulting gap.

Prior to the time when direct attack on an aortic lesion was available, sympathectomy was the only surgical procedure which could be offered these patients. On a theoretic basis, there might be areas in the upper and midportions of the body in which the relaxation of arterial tone could reduce the resistence in the total peripheral vascular bed to the point of bringing some benefit. While some favorable results have been reported for lumbodorsal

sympathectomy, it is now the general impression that sympathectomy is of little value. It certainly has less to offer than the surgical attempts at restoration of a normal aortic pathway.

After careful experimental animal work, Blalock and Park[3] suggested a form of treatment for human coarctation by severing the left subclavian artery high in the chest and turning it downward for a direct union to the segment of aorta which is distal to the point of obstruction. This technic can be carried out, leaving the coarctation in place, and anastomosing the subclavian artery to the aorta in an end-to-side manner. It is preferable, however, to remove the aortic obstruction so that an anastomosis between the subclavian and the distal aorta can be made by an end-to-end union. The size of the pathway thus established may be considerable, when one recalls that the left subclavian artery (in the presence of coarctation) is usually quite dilated. There are two possible drawbacks to such an undertaking: (1) The severance of a subclavian artery cuts off a large number of collateral channels, the loss of which is not inconsequential. (2) The base of a subclavian artery is sometimes semirigid, so that attempts to turn the vessel downward result in a kinking which greatly reduces the size of its lumen. My own experience with the technic has been limited, as is noted in the following section; the results were fair but certainly were not perfect. Personal communications from Dr. Clagett at the Mayo Clinic and from Dr. Blalock with his Hopkins' series indicate that, while a fair result occurs in many subjects, there are some in whom the relief of hypertension is excellent. I believe, however, that most surgeons would agree it is preferable, whenever possible, to anastomose directly the two ends of an aorta and to reserve the subclavian technic for those situations in which it is impossible to complete the more ideal procedure.

A third operative approach—and probably the one which will have the greatest usefulness—is an excision of the narrowed aortic segment and reconstruction of the pathway by bringing together the remaining ends of the aortic tube. Experiments published from our laboratory indicate that this is a technically sound undertaking. Crafoord and Nylin[9] earlier, and now a number of other surgeons, have been able to show that this operation, while formidable, can be completed with reasonable mortality rates. It is not appropriate to discuss technical details in this article, but a few points and general principles are well worth stressing. It is important to emphasize that if these operations are going to prove successful in long series of cases it is necessary to insist that *all* of the coarctation must be removed. Under the stress of operation it is quite tempting for the surgeon to cut away only the more narrowed part of the constricted area, because he is fearful that more radical excision would lead to difficulties in approximation of the remaining vessel-ends. Such a compromise is very apt to be followed by incomplete relief of hypertension. To obtain the best possible results, every effort must be made to remove *all* of the constriction and to establish a pathway which is fully the size of the aortic arch (figs. 2–4).

In the first part of this work, it was my custom to sever one or two sets of intercostal arteries below the point of obstruction to facilitate mobilization of the aorta and to make easier the handling of the lower aortic end during the subsequent stages of suturing. Crafoord and Blalock are both quite correct in emphasizing that these collateral channels should be saved if possible. In most cases the thin intercostal arteries can be raised from their beds and can be temporarily occluded by small serrefine clamps without hampering too much the subsequent stages of operation on the aorta itself. However, there are occasional subjects in whom intercostal arteries enter the aorta immediately subjacent to the obstruction and it is imperative to divide one or two of these arteries to develop an aortic cuff with which to work. While it is now general practice to preserve intercostal arteries whenever possible, it must be recognized that there are some anatomic arrangements which require sacrifice of one or two of them to permit establishment of a first-rate aortic union.

There is little room for argument when discussing the various methods of reconstruction of an aortic tube. Crafoord has attempted to

unite the individual layers of the wall, whereas I emphatically prefer a technic whereby intima is brought to intima and the ends of the vessel are everted. Overwhelming evidence from laboratories and also from operations on human subjects indicates that the latter is a far superior procedure, is easier to perform, and carries less chance of postoperative disruption or aneurysm formation.

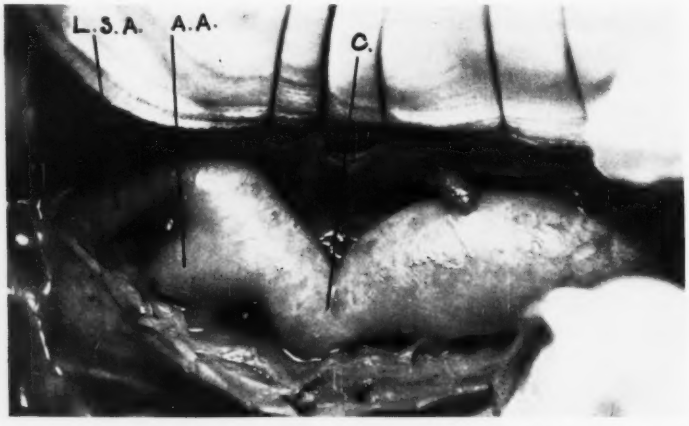

FIG. 2.—Photograph of coaretation, taken at the operating table. The aorta is constricted, and it has an angulation due to the pull of the ligamentum arteriosum which lies buried beneath it. The indented zone is quite thick (by palpation) indicating that only a tiny opening exists at this level (see fig. 3). The aorta below the block is larger than that above it—a common finding. A.A., Aortic arch. C., Coarctation site. L.S.A., Left subclavian artery.

The position of a coarctation has much to do with the ease or the difficulty with which it can be excised. Obviously, the surgeon's troubles are least when the block lies well below the origin of the subclavian artery so that a segment of the descending aorta (above the block) is available for manipulation, clamping, sewing, and like procedures. Unfortunately, many obstructions are at a very high level—just beyond the origin of the left subclavian artery—and in a few cases may actually be in the distal part of the arch itself. With such anomalies the surgeon's difficulties are tremendously increased, particularly when dealing with older subjects in whom the vessels are rigid. While high strictures should be approached with more caution and apprehension, they do not necessarily present an insuperable problem. Fifteen patients of the present series had a block just at the origin of the left subclavian artery, and to obtain a proximal stump it was necessary to place a clamp directly across the aortic arch and across the left subclavian artery so that the latter was occluded temporarily. To facilitate matters with this particular anatomic arrangement, Blalock[2] has revamped a Pott's aortic clamp in such a way that it can be placed with a high degree of safety across the distal part of the arch and subclavian artery; it will give a proximal cuff to work with, and at the

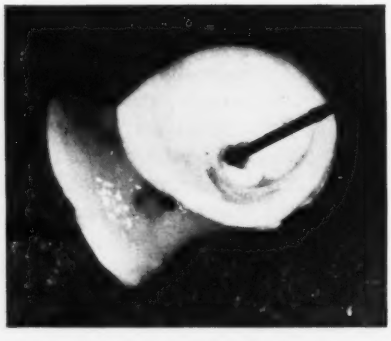

FIG. 3.—Photograph of specimen removed from indented area shown in Fig. 2. The orifice barely admits a hairpin probe. (In our entire series of excised coaretations, the orifice varied from 1 to 3 mm. in diameter, excepting in 7 patients in whom there was a complete diaphragm).

same time it will allow a small amount of blood to flow into the subclavian artery during this stage of the operation while the clamp is in place.

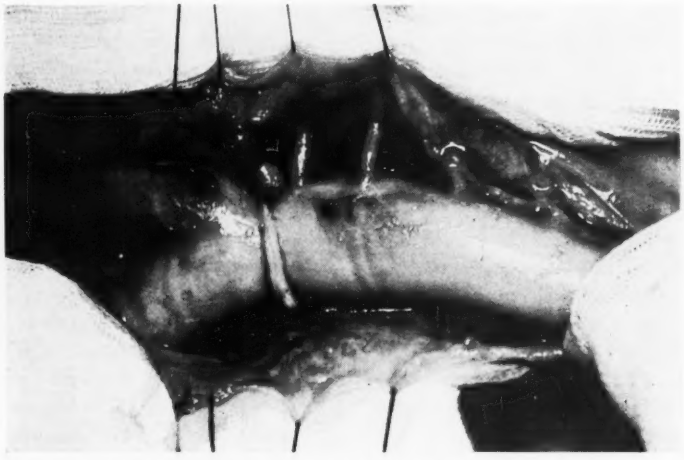

FIG. 4.—Photograph from same case as figure 2, after excision of the coarctation and end-to-end reconstruction of the aorta. The lumen at the anastomosis is fully the diameter of the aortic arch.

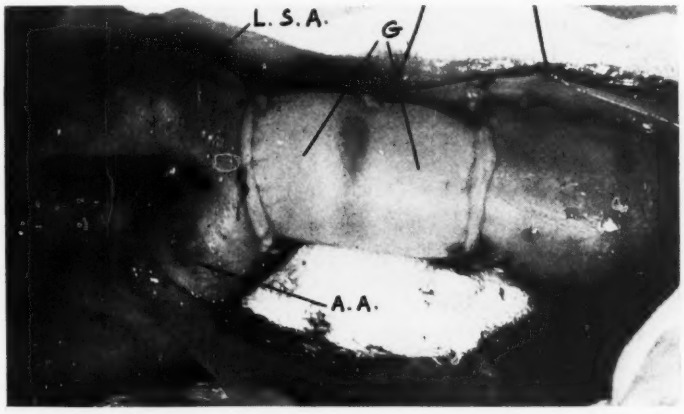

FIG. 5.—Photograph taken at completion of operation showing an aortic graft which was used to bridge a large gap left after removal of a long coarctation. An excellent aortic pathway has been established. A.A., Aortic arch. L.S.A., Left subclavian artery. G., Graft. The graft was 5 cm. in length.

Finally, a fourth type of procedure is now available for treatment of coarctation which is particularly useful for those cases in which the narrowed segment is very long; it is likewise valuable in adults wherein the removal of even a short aortic segment presents the surgeon with problems, because the remaining aorta is rigid and the ends cannot be easily brought together. The insertion of a graft makes it possible to re-establish the aortic pathway (fig 5). Extensive laboratory work (on dogs) has shown[14] that it is possible to transfer an aortic segment from one animal to another, to have it survive, and to have it serve as an excellent pathway. Such grafts have been implanted in recipient animals and observed for periods as

long as two years. The risk of dilatation or aneurysm formation appears to be almost nil. The grafts do show some degenerative changes, but they carry blood in a highly satisfactory manner. While observations from animal work do not necessarily indicate what will happen if aortic segments are transferred from one human being to another, there seemed to be sufficient experimental background to justify trials of them in human subjects to bridge large arterial gaps which could not be treated by any other means.

Aortic segments have been gathered from human beings who have died in an aseptic fashion (accidents of various sorts) and this material has been used to bridge the defects which have been left after excision of coarctations. These grafts have varied from 4 to 5 cm. in length. Six of them have been inserted; the patients have been followed from three months to one and one-half years.

Results of Operations

Scrutiny of the results of surgery must seek to answer three main questions: (1) What are the risks of surgical therapy? (2) To what degree has hypertension been relieved? (3) Which of the several available forms of operation is most apt to produce a favorable end result?

Of our 100 patients, 9 had only an exploration. The findings within the chest were such that it seemed wiser to withdraw than to persist in some therapeutic attempt which might lead to disaster. In some of these the vessels were very rigid or else they were fixed in their beds as a result of previous, burned-out infection. In others, the constricted portion of the aorta was unusually long and removal of it would have required a graft which was not available at the time. Without doubt, the number of exploratory operations can be greatly reduced in the future if a supply of grafts can be kept on hand and ready for use when the occasion demands.

In the present series of 100 patients with coarctation who have been operated upon, there have been 11 deaths either at operation or in the postoperative period. These are listed in table 1. In this table, the first 4 cases which are grouped together represent types of complications and fatalities which are likely to be met again in this type of surgery and which constitute a risk which is probably unavoidable. In the lower portion of the table are listed cases with fatalities which we now feel can be prevented by certain changes in surgical technic or which can be avoided by declining operation when there are certain coexisting cardiovascular complications.

Table 1.—*Causes of Death in 100 Coarctation Operations*

Case	Age	Coexisting disease recognized before operation	Cause of Fatality
	years		
1	30		Arteriosclerotic aorta. Hemorrhage and sudden death in 24 hrs.
2	15		Intracranial hemorrhage during operation. Death 3 days later
3	19		Fatal hemorrhage on table from torn intercostal artery
4	9		Cardiac arrest during operation. Decerebrate. Death 36 hrs. later
5	7		Too sudden removal of clamps
6	14		Sudden death at end of operation, probably due to cyclopropane
7	9	Rheumatic mitral stenosis	Congestive failure. Death 6 days after operation
8	16	Right bundle branch block	Cardiac failure. Death 4 days after operation
9	21	Bicuspid aortic valve with insufficiency	Sudden death 14 hrs. after operation
10	19	Delayed A-V conduction	Sudden death as chest was opened
11	17	Rheumatic mitral stenosis	Congestive failure. Death 4 days after operation

In the fifth case (table 1), a rapid removal of the aortic clamps allowed blood to rush suddenly to the lower part of the body where it pooled; blood did not return quickly enough

to supply a circulating medium. Such a death from "shock" we now know can be prevented by allowing the readjustments in the system to take place more slowly over a period of several minutes. In the sixth case, operation was completed without the slightest apprehension, but as the anesthetic mask was removed there was sudden collapse and death: a fatality which was thought to be due to cyclopropane. While this anesthetic agent has some apparent advantages for certain chest operations of short or medium duration, it is probably dangerous and should not be used for long procedures such as surgical correction of a coarctation. In Cases 7 to 11, inclusive, the deaths were all quite clearly related to a complicated cardiovascular picture. In each of these patients, the coexisting cardiovascular abnormality was recognized before operation. While we have had one patient with rheumatic mitral disease and coarctation of aorta survive operation on the latter, the two fatalities listed here raise a serious question regarding the advisability of attempting any more operations under such circumstances. The two deaths in patients with disturbances in the conduction system emphasize the importance of careful study of electrocardiographic tracings and the refusal of operation for anyone in whom such disorders are found to exist. Finally, bicuspid aortic valves are known to be a rather frequent abnormality in patients with coarctation of the aorta. A double-leafed valve in itself carries little additional surgical risk, but if there is any important degree of regurgitation the chances of a sudden fatality are probably very high. I now believe that operations for correction of a coarctation should be avoided in all persons who have important rheumatic valvular disease, serious conduction system disorders, or advanced degrees of aortic insufficiency. In summary, the operative mortality in this series of 100 patients has been 11 per cent, but the suggestions herein noted will probably make it possible to reduce the rate in the future to 5 or 6 per cent.

There has been one late death following surgery. This occurred in a 22 year old man who obtained a satisfactory relief of hypertension by removal of his coarctation. A routine, check up, chest film nine months after surgery showed no unusual findings. One year after operation there was onset of chest pain and hemoptysis; at this time a roentgenogram showed a fist-sized mass in the chest to the left of the spine which almost certainly represented a hematoma near the operative site. Presumably, bleeding had occurred from one of the thin-walled intercostal arteries in the area, or more likely had come from the aortic suture-line itself; erosion into the nearby lung accounted for the hemoptysis. With bed rest, sedation and transfusions the bleeding subsided, but was followed a few weeks later by a fatal hemorrhage.No autopsy examination was allowed. (Routine, long-term postoperative chest roentgenograms have not been obtained in all of our patients, but in those studies which we have made no dissecting aneurysms have been found.)

In evaluating postoperative states we are concerned most with objective evidence of what has been accomplished. Study of the blood pressure changes affords the best record of the readjustments which have been made in the circulatory system. The relief of hypertension is the main purpose of the surgical attack, and observations indicate that it is possible to reach this goal in a very high percentage of cases. Removal of an aortic block seldom results in a precipitous fall of the arm pressures. Though we have seen the arm pressures return to normal within twenty-four hours in a few individuals, the more common reaction is to have a gradual distension of the vascular bed in the lower part of the body during a period of two to three weeks, and concomitant with this there is a progressive fall in the arm pressures. Generally, the maximum benefit is manifested by the end of several weeks; if relief of hypertension has not been obtained in this period it is usually wishful thinking to anticipate that it will occur in the more distant future.

Follow-up studies on our 80 patients who have survived excision of a coarctation show the results which are summarized in table 2; these patients have been followed for periods varying from two months to as long as four years since operation. In one young man, 19 years of age, there was no lowering of brachial pressure: a fact which was anticipated at the termination of operation because technical

difficulties made it impossible to establish any satisfactory opening at the site of anastomosis. In 8 other subjects there has been a very decided drop in arm pressures, but they have not returned to completely normal figures; these can be classed as "satisfactory," but not as complete cures. In this group are several pleasing results: drops in arm pressures from 200 or 210 systolic down to 155 or 160. In each case, an aortic pathway was established which was 10 to 15 mm. in diameter, but obviously was not as large as the aorta above or below the area. These observations again give emphasis to the point that *all* of the narrowed aorta must be removed (and not merely the middle portion of the constricted area) if ideal results are to be expected. Finally, 71 patients had complete relief of their hypertension; by this is meant that arm pressures in adults have fallen below 140 systolic and that in children the pressures are even lower and are in ranges which are regarded as normal for their respective ages (fig. 6).

TABLE 2.—*Results in 80 Patients who Survived Excision of a Coarctation*

No relief of hypertension	1
Fairly satisfactory relief of hypertension	8
Complete cure of hypertension	71
Total cases	80

In judging the results of surgical therapy for coarctation of aorta, some mention must be made of the types of operative procedures employed and the impressions gained regarding their effectiveness in producing desired results. In the present series, three types of undertakings were employed for the surviving 80 patients. My experience has been limited with the technic suggested by Blalock and Park[3] of turning down the left subclavian artery for anastomosis to the distal aorta. It was employed twice; there was only partial alleviation of the hypertension, in spite of the fact that the subclavian artery in each instance was huge and I had expected to establish an excellent aortic channel. The somewhat disappointing results were presumably due to the fact that much pre-existing collateral flow must have

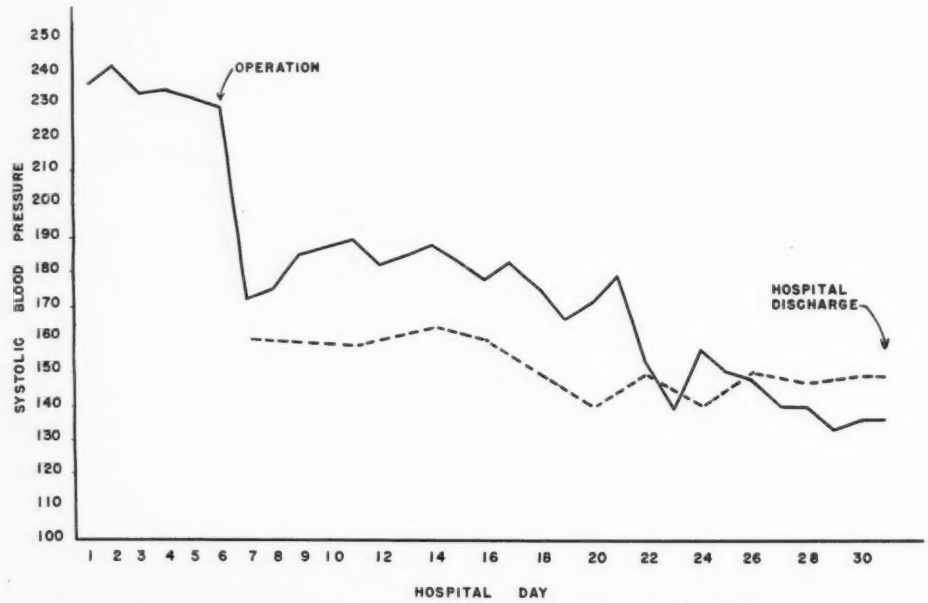

FIG. 6.—Blood pressure chart from a 12 year old boy with coarctation of the aorta who was treated by excision of the stricture, followed by end-to-end anastomosis of the remaining aortic ends. Solid line indicates the systolic arm pressures and the dotted line shows the systolic leg pressures.

been disrupted by severence of the subclavian artery and furthermore the full caliber of the vessel could not be utilized, because the structure became kinked and angulated when turned into a new direction.

Excision of a coarctation and repair by end-to-end union of the aorta seems by all odds to be the operation of choice; when it can be performed it gives the best chance of producing a channel of large size and is the one which is most apt to remain open. The favorable outlook for persons on whom this operation has been completed can be gleaned from the statistics in table 3. In 7 of these patients a patent ductus arteriosus was simultaneously treated by complete division and closure of this structure. There are some subjects in whom it is difficult or impossible to remove a coarctation because the constricted area is long, or else the aorta is inelastic and cannot be stretched to overcome anything more than a minimal gap. The surgeon's ingenuity may be taxed to the limit, but increasing familiarity with surgical work of this kind makes it evident that more and more success is being obtained in cases which several years ago would have been regarded as inoperable. Whenever a primary anastomosis cannot be done, the surgeon has the alternative of turning down the subclavian artery, or better still of implanting an aortic graft.

Grafting of aortic segments from one human being to another is still in the early stages of development; hence no definite statements can be made regarding its ultimate usefulness. The early results are quite promising in the 6 patients who are alive three months to one and one-half years after insertion of such grafts. Following operation, all of these subjects have had a marked rise of pressure in the legs, an appearance of satisfactory femoral artery pulsation, and a disappearance of hypertension in the upper part of the body. One is not justified in making any predictions about the fate of these grafts over a period of several decades, but the findings thus far make me very desirous of using more of them for patients in whom it is impossible to re-establish the aortic pathway by direct suture of its ends.

Accurate statistics regarding postoperative changes in murmurs have not been gathered, but certain impressions have developed which are probably worth recording. In a relatively small proportion of patients, all murmurs have disappeared. In the vast majority of cases, murmurs have persisted but have been reduced in intensity. In a few instances they have changed but little. These observations cannot always be explained adequately. In some circumstances a slight narrowing might have been left at the anastomotic site which could still set up a swirl and a murmur, but yet there are other patients who have been given an aortic lumen of full size and smooth contour, who likewise have postoperative murmurs. These sounds can originate from angulated, tortuous collateral channels, bicuspid aortic valves, septal defects, and the like—and it is obvious that most of them will persist after removal of the aortic anomaly.

TABLE 3.—*Types of Operation and Respective Results in Surviving Patients*

Type of operation	No relief of hypertension	Fair relief of hypertension	Cure of hypertension	Total number of cases
Excision of coarctation of aorta: subclavian to aorta		2		2
Excision of coarctation of aorta: end-to-end suture of aorta	1	6	65	72
Excision of coarctation of aorta: insertion of aortic graft			6	6

Postoperative changes in certain subjective symptoms are worthy of comment. Almost all of the subjects who had headaches preoperatively have volunteered the information that these have disappeared. Many patients notice increased strength and warmth in their legs, along with a disappearance of the cramps which formerly existed. A few subjects who before operation had considerable pain in the precordium, left shoulder or left arm, have now been greatly or completely relieved of this distress. This change is particularly striking in one 21 year old mother who had become addicted to morphine; following operation the alleviation of pain has been so marked that she

has ceased using all drugs and is now carrying on her household duties.

Summary

Coarctation of the aorta can be recognized with a high degree of accuracy by physical signs which are easy to elicit and by roentgenologic studies of a rather simple sort. The condition is compatible with a long life in some instances, but serious complications or fatalities are found in the majority of cases. Of all patients possessing this abnormality the average age at death is about 35 years. Of those who die from complications directly related to a coarctation the average age at death is about 30 years. The principal causes of death have been aortic rupture, superimposed bacterial endocarditis or aortitis, intracranial hemorrhage, and hypertensive cardiac failure.

Laboratory investigations have clearly indicated that portions of the thoracic aorta can be removed and that the aortic pathway can be reconstructed by direct suture of the remaining ends of the vessel. In human beings with coarctation, it is likewise possible in most instances to excise the aortic block and join the remaining aortic ends. Patients in whom excision of the constriction leaves a very long gap, or those in whom rigidity of the remaining aorta makes it impossible to overcome a short gap, can be treated by the insertion of an aortic graft. In a small number of grafts which have been employed to date the results are very satisfactory during the time interval that they have been followed (up to one and one-half years).

In a series of 100 patients with coarctation who have been operated upon the results can be summarized as follows: Nine had only thoracic exploration; the findings in the chest were such that it seemed too risky to attempt removal of the aortic stricture. There were 11 fatalities from various causes. Seven of these deaths would now be regarded as avoidable by changes in operative technic which have currently been adopted, and by refusal to operate in certain complicated types of cases in which the risk is exceedingly high. It is reasonable to expect that the surgical mortality rate can be reduced to 5 or 6 per cent in the future. Of the 80 patients who survived operation, one had no relief of hypertension, 8 had fairly satisfactory relief, and 71 had complete disappearance of hypertension. Surgical therapy for coarctation appears to be on a sound basis and has a great deal to offer most persons who are afflicted with this abnormality.

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Effect of Changes in Posture on Peripheral Circulation, with Special Reference to Skin Temperature Readings and the Plethysmogram

By R. H. Goetz, M.D.

Effects of changes in posture upon plethysmogram and skin temperature are investigated. Since posture, by altering venous return, affects pulse volume and response of digital volume and skin temperature to procedures releasing sympathetic tone, these should not be interpreted solely in terms of arterial blood flow. In the normal elevated limb, e.g., the skin temperature response to body heating simulates organic arterial disease. The clinical significance of these findings is discussed with particular reference to interpretation of skin temperature readings, the diagnosis of thromboangiitis obliterans, indications for sympathectomy in poliomyelitis, the management of the edematous limb and other conditions.

ALTHOUGH there is an extensive literature on the response of the circulation in general to changes in posture, very little has been reported so far as to the changes caused by posture on the *peripheral* circulation in a strict sense. In man, assuming the erect position produces a rise in the general blood pressure (particularly in the diastolic blood pressure), increases the heart rate, and produces a decrease in the plasma volume by about 15 per cent.[1–4] With regard to the cardiac output, numerous authors[3, 5–7] have reported that assuming the erect posture will decrease the minute volume, although this observation has been questioned by Grollman[8] and by Goldbloom and associates.[9] It is well known that prolonged quiet standing puts a severe strain upon the circulation, as demonstrated by the frequency of fainting. While some animals die from cerebral anemia if kept upright,[10] others, especially man, may alter their posture from the horizontal to the erect without impairment of the circulation. This, almost of itself, suggests that there must exist certain mechanisms of adaptation, since the blood would otherwise tend to accumulate in the most dependent parts. Most persons have experienced some degrees of swelling of the legs on long, quiet standing; indeed, this has been demonstrated scientifically by numerous workers.[2, 11, 12] Atzler and Herbst[13] calculated that about 500 cc. of extra blood may accumulate in the legs during quiet standing for one hour and Grill[14] found the increase to be 4 per cent of the leg volume.

Obviously, the marked changes in hemodynamics, particularly the increase in hydrostatic pressure, which result from the assumption of the upright posture, produce profound changes in the peripheral circulation and set in train definite mechanisms of adaptation on the part of the peripheral vessels. Bock, Dill, and Edwards[15] demonstrated that the acceleration of the heart rate normally observed following the injection of histamine into an ankle vein takes twice as long if the subject is erect than if recumbent. That this is not due solely to an increase in the cross-section area of the vascular tree caused by a distention of the vessels by the hydrostatic pressure is suggested by the reduction in the oxygen saturation in the blood of the femoral vein during maintenance of the erect posture, as reported by Florken, Edwards, and Dill.[16] This suggests that there is a reduction in the blood flow through the lower extremities in the erect posture, and indeed this has been demonstrated phethysmographically by Proger and Dexter.[17] Doupe and his collaborators[18] pointed out that the increase in venous pressure in the dependent posture results in an increase of venous tone (venous stretch reflex) which is abolished on elevation due to the drop in venous pressure, causing relaxation of the peripheral blood vessels. It is the venous stretch reflex which prevents the pooling of blood in the upright posture. We ourselves[19, 20] have already demonstrated that

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changes in posture markedly influence the peripheral blood flow, as judged by the plethysmographic record, although at the time we did not go into any detail.

Methods and Material

The methods used in this study followed closely those previously described and the reader is referred to earlier articles.[19–21] Continuous records of the peripheral blood flow were obtained by using our digital plethysmograph. In this the digit is enclosed within a glass cup which is connected to a pipet, graduated in 0.01-cc. units, containing a column of alcohol. When the plethysmograph is sealed with petrolatum and the tap closed, the volume changes in the digit are transmitted to the alcohol column, the movements of which are enlarged and projected onto the paper of a recording camera. Since the publication of a preceding article,[19] the method has been perfected in such a way that now two pipets are mounted next to each other and thus it is possible to record simultaneously the changes in peripheral blood flow of two digits, either of the same or of different extremities. A portable model has been constructed as well.[20, 36] This plethysmographic method is capable of exact and undistorted measurement of the changes in skin volume, and differences of 0.001 cc. are recorded easily. In many films the respiratory changes or the skin temperatures (determined by means of thermocouples) were recorded simultaneously with the plethysmogram. The rate of blood flow was obtained by means of the venous congestion test previously described.[19, 22] In this the pressure in the obstructing cuff is recorded on the film by means of a Frank capsule. All observations were conducted in a draught-free, noiseless room. The room temperature was kept constant during the experiments. The investigations were carried out on 24 normal subjects, 6 patients with thromboangiitis obliterans, and 8 patients with venous thrombosis of the lower extremities. Although the investigations were conducted almost exclusively on the lower extremities, investigations in the upper limbs confirmed the findings and did not suggest that there was any difference between the reaction of the upper and lower limbs. The tests were performed after thirty to sixty minutes' rest.

All our published investigations (previously reported) as well as all diagnostic tests at Groote Schuur Hospital have always been carried out with the patient resting on a special type of couch (fig. 1, *A*) or on a surgical bed with the subject in a similar position. Patients investigated in this position are referred to as "reclining." In order to determine the effect of elevation on the circulation through the lower limbs, the patients were examined in a position indicated in figure 1, *B*, in which the back of the couch was lowered and the legs elevated to an angle of about 45 degrees above the horizontal. Limbs tested in this position are referred to as "elevated." In addition, patients were investigated sitting on an ordinary chair or standing. The position is noted in each of the figures. A number of tests were carried out on the tilting table in the x-ray department, using the portable plethysmograph.*

Fig. 1.—*A*. Examination couch as developed in our laboratories for plethysmographic examinations. The footrests and back of the couch are adjustable. The back can be lowered so as to be used as an ordinary examination table. The arm bath is on a movable stand. (By courtesy of the South African M. J. **22:** 391, 1948.) Patients tested in this position are referred to as "reclining."

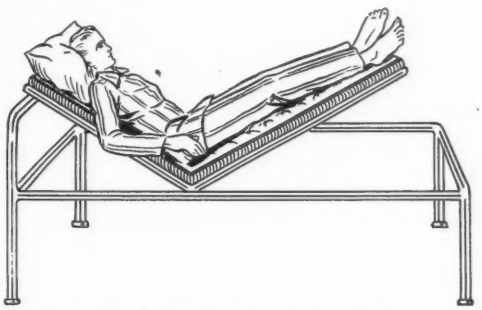

Fig. 1—*B*. Position of patient referred to in text as "elevated" with reference to lower limbs.

*Manufactured by Hilger & Watts, London.

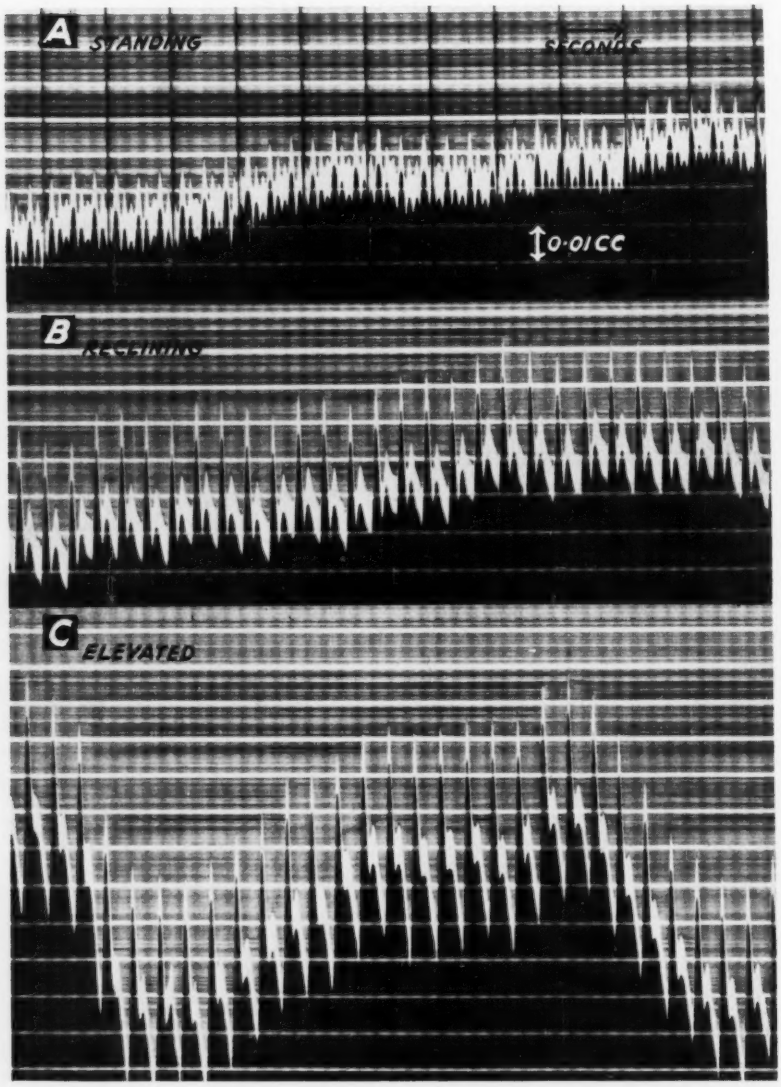

FIG. 2.—Effect of posture on shape and height of pulse volume of first toe (fully dilated) of left foot. *A*. Standing; *B*. reclining (as indicated in fig. 1, *A*); *C*. elevated (as indicated in fig. 1, *B*). (For explanation see text.) Height of pulse volume in *A* is ±0.012 cc.; in *B*, ±0.03 cc.; and in *C*, ±0.05 cc.

Reflex vasodilatation of the peripheral vessels was obtained by immersing one upper limb into water of 45 C. temperature for thirty minutes and covering the subject with blankets so as to prevent the dissipation of heat. A special thermostatically controlled tank for this procedure had been developed.[20, 35] (See fig. 1, *A*.)

RESULTS

Effect of Posture on the Pulse Volume in the Normal Subject: The pulse volume of the normal subject (figs. 2, *B* and 3, *B*) resting in the reclining position consists of the main systolic elevation followed by a dicrotic wave; occa-

sionally there may be a minute and insignificant accessory wave. With elevation of the limb (figs. 2, *C* and 3, *C*) the following changes are observed: the main systolic elevation becomes higher, the dicrotic wave smaller, and the accessory waves disappear. Consequently, the incisura or notch between the systolic and the dicrotic wave is usually less marked and often disappears completely. In some subjects, especially when the vessel is fully dilated, there may be no dicrotic wave and a typical monocrotic pulse is registered (fig. 3, *C*). The opposite occurs as a more dependent posture is assumed. With the subject sitting (fig. 3, *A*) or standing (fig. 2, *A*), the main systolic elevation becomes smaller, the dicrotic wave more prominent, and one or two well developed accessory waves follow. The result is that three or four waves become registrable (fig. 2, *A*). On standing, the notch between the first (systolic) elevation and the following dicrotic wave normally reaches the base line, when, in consequence,

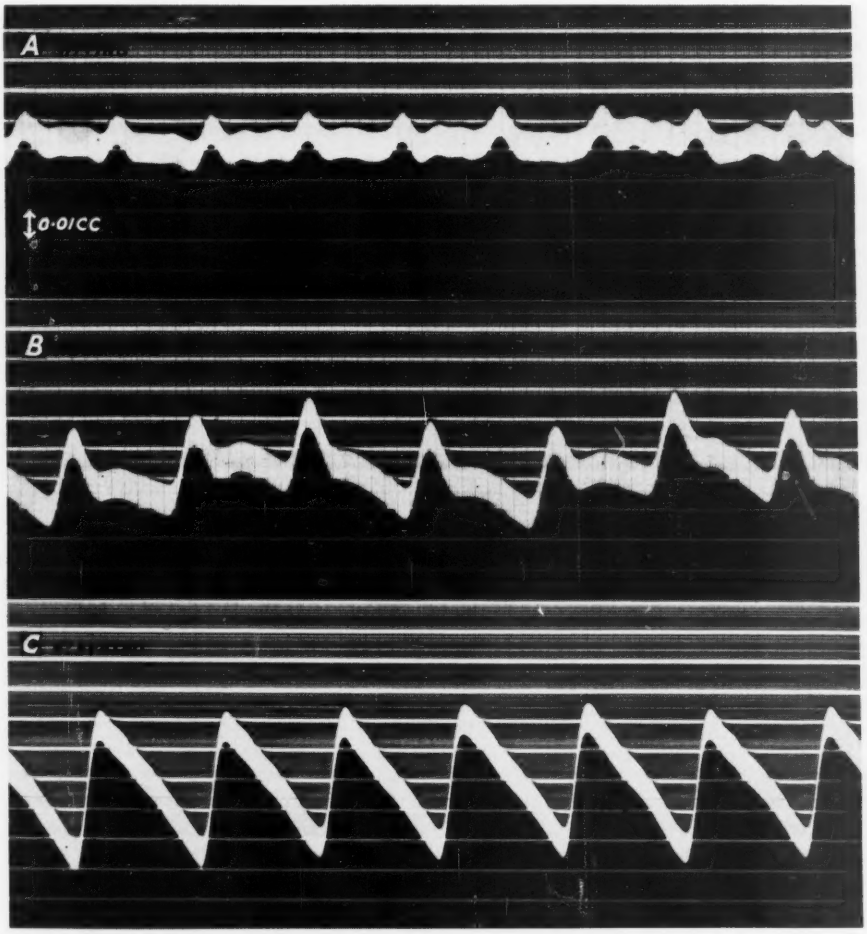

FIG. 3.—Plethysmogram, taken at fast speed, showing the changes in the shape and height of the pulse volume in various postures. *A*. Sitting; *B*. reclining; *C*. elevated. Height of pulse volume in *A* is ±0.01 cc.; in *B* ±0.02 cc.; and in *C*, ±0.04 cc.

three to four waves often of equal size may be recorded. In such cases it may be difficult to recognize the individual pulse volume, particularly if the vessels are constricted and the pulse small.

The changes in pulse volume which take place with changes in posture can be followed easily if a continuous record is taken while the patient is being tilted from the horizontal to the erect posture (fig. 6).

Even small changes in posture have a profound effect on the shape of the pulse volume, as indicated in figure 4. In this figure the pulse volume of two toes is registered simultaneously. The lower record was obtained from the limb resting in the horizontal posture, while the upper record refers to the limb kept at an angle of about 45 degrees below the horizontal. The differences in the height and shape of the pulse volume are recognized easily.

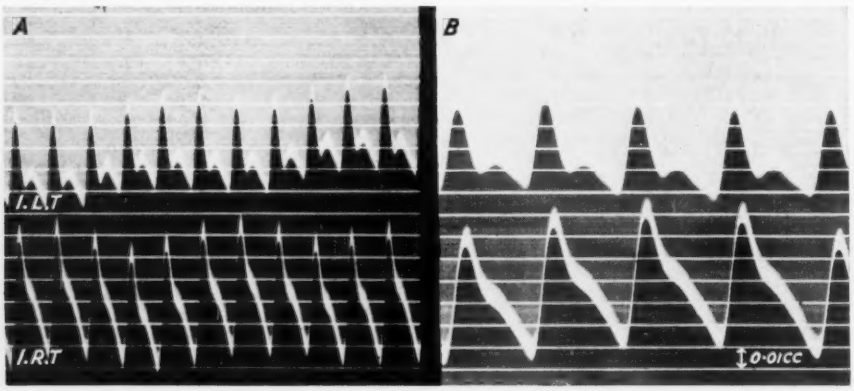

FIG. 4.—Plethysmogram of first toe of left foot and first toe of right foot simultaneously recorded. The left limb (upper tracing) was tested at an angle of 45 degrees below horizontal. The right limb (lower tracing) was kept in the horizontal posture. Note the differences in the height and shape of the pulse volume even with such slight differences in posture. *A* at usual and *B* at fast speed to show the exact shape of pulse volume.

In addition to these changes in the height and the shape of the individual volume pulse, posture has a marked effect upon the spontaneous changes seen normally in the height of the pulse volume which reflect the changes in central vasomotor tone.[19, 22] During sitting and standing the pulse volume hardly changes. However, as the legs are elevated, changes in the height of the pulse volume become more and more marked and when the leg is fully elevated they are extremely prominent (fig. 2).

Changes in Digital Volume due to Changes in Posture in the Normal Subject: As has been pointed out previously,[19] spontaneous changes in digital volume observed during rest are mainly a function of changes in pulse volume. From this it follows that during elevation, changes in digital volume are more prominent than during sitting and standing, when hardly any changes in digital volume may be recorded (fig. 2). As the limbs are elevated, the changes become more marked and in those subjects who naturally show well developed fluctuations in vasomotor tone, spontaneous changes are very pronounced if the legs are elevated. But even small differences in posture will have an appreciable effect on the fluctuations in digital volume (fig. 5). When the tracing shown in figure 5 was taken, the patient was reclining comfortably, the one limb (upper tracing) being held in a slightly pendent posture with the knee flexed at an angle of 45 degrees against the horizontal. The other limb (lower tracing) was kept slightly elevated at an angle of about 30 degrees above the horizontal. The changes in digital volume of the slightly elevated limb are far more pronounced.

Similarly, all extrinsic and intrinsic stimuli

which normally produce a fall in digital volume, such as a deep breath, an unexpected noise, mental strain, etc., elicit a much more pronounced response in an elevated than in a dependent limb.

Abramson and Katzenstein[23] reported that spontaneous fluctuations in the plethysmogram are characteristic for the hands but are absent or insignificant in the lower extremities. The present investigations go to prove that this difference is not due to any difference in vasomotor tone but is caused by differences in posture. The lower limbs obviously were tested in the dependent posture by these authors, which, as the present investigations show, accounts for the differences recorded. As we have pointed out,[19] spontaneous changes in blood flow are characteristic for both the upper and the lower extremities, and if tested under identical conditions they are of the same magnitude in both upper and lower limbs.

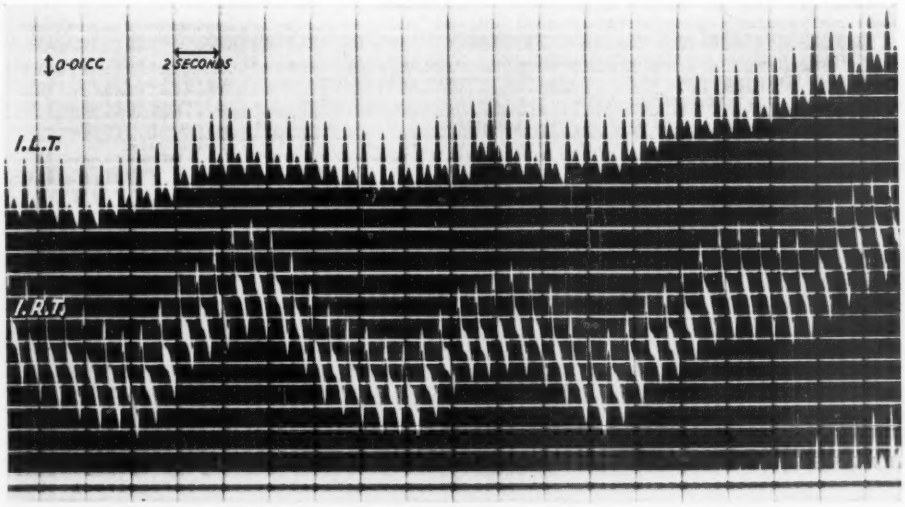

FIG. 5.—Plethysmogram of first toe of left foot (upper tracing) and first toe of right foot (lower tracing) simultaneously recorded to demonstrate differences in the height of spontaneous fluctuations as caused by differences in posture. The left limb was kept slightly dependent; the right limb was in a slightly elevated position. (For explanation see text.)

The changes which occur both in digital volume and pulse volume as the subject changes from the horizontal to the vertical are easily followed in figure 6, which was obtained by tilting the subject on an x-ray examination table. At the signal, tilting is commenced and instantaneously there occurs a rise in digital volume similar to that obtained on inflating a cuff and obstructing the venous return. The digital volume rises approximately 0.3 cc., which means that the total volume of the digit is increased by about 2 per cent. The typical changes in both the height and the shape of the pulse volume, as described before, are observed. The pulse volume, which registered 0.03 cc. in the horizontal position, reaches barely 0.01 cc. in the erect position. The reverse is seen on returning from the horizontal to the erect posture. The digital volume decreases by the same amount and the pulse volume returns to its original height. All the changes registered both in pulse and digital volume with tilting and described for the normal were obtained in the sympathectomized limb as well.

Pulse Volume in Cases of Venous Obstruction and Thromboangiitis Obliterans: That the knowledge of the effect of changes in posture upon the plethysmographic appearances may not only be of academic interest but of practical value was made clear to us for the first time six years

ago when we tested a patient in whom extensive thrombosis of the veins of one leg had occurred following the injection of a quinine compound. This patient showed no clinical signs of arterial disease. He was tested like all other patients in the usual *reclining* position indicated in figure 1, *A*. However, the pulse volume showed all the characteristics of the pulse volume obtained in the normal subject with the volume at fast speed (fig. 8, *A*) was it realized that there was a definite pattern recorded which was the pulse volume. It was then that the thought occurred to us that the interference with the venous drainage might account for the picture. The leg was therefore elevated to an angle of 45 degrees and the pulse volume recorded in this posture featured the normal dicrotic pulse (figs. 7, *B* and 8, *B*).

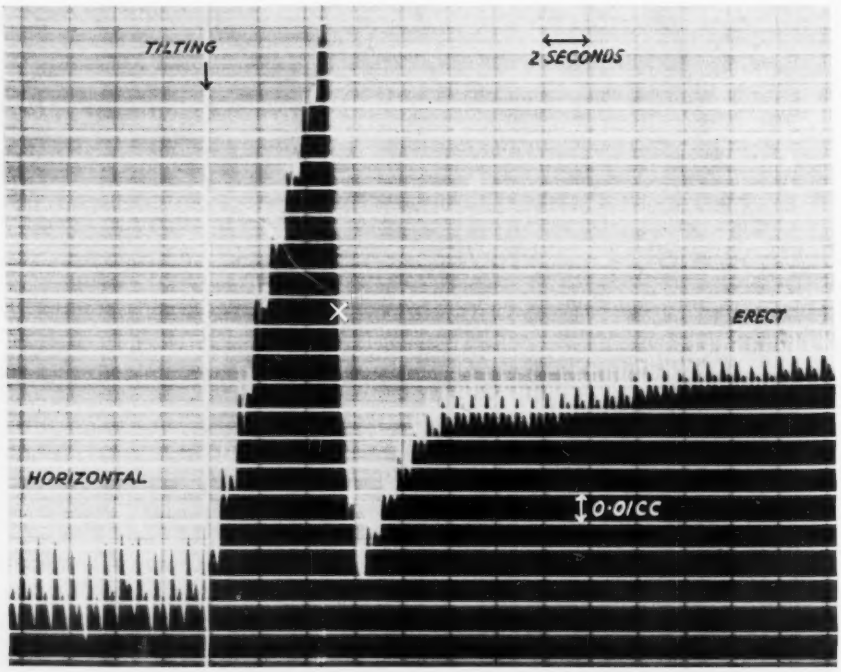

FIG. 6.—The effect of changing the posture of a limb as produced by tilting, on the peripheral blood flow in a normal subject. Note the increase in digital volume on tilting the patient from the horizontal to the erect posture, the decrease in pulse volume from 0.03 to 0.01 cc., and change in shape of pulse volume. (For explanation see text.) The "X" on the tracing indicates the point at which the plethysmogram was adjusted.

limb in *pendent* posture (fig. 7, *A*). Each pulse was composed of three well developed waves, the notch between each of them being very marked and reaching the base line between the first and second (dicrotic) wave, making it extremely difficult to pick out the individual pulses. Actually, the tracing was first considered to be produced by a coarse tremor and not to represent the pulse volume at all. Only on special scrutiny and on recording the pulse

An identical picture was later obtained in a young woman in whom thrombosis of the inferior vena cava had been diagnosed (fig. 9). Here, too, although the pulse volume recorded in reclining posture was extremely small, it featured three well developed waves of almost equal size which at first sight were regarded as a fine tremor, but on close examination it was realized that the same pulse pattern was presented as that seen in the normal subject in

the erect posture. When the leg was elevated the normal shape in pulse volume was observed (fig. 9, *B*).

It had long been observed by us that the pulse volume in a high percentage of patients with thromboangiitis obliterans, when tested in the reclining posture, showed the pattern normally recorded in pendent posture. Such a tracing was demonstrated in figure 13 in our paper on the rate of blood flow published in 1943.[22] Figure 10 of the present article was obtained from 2 patients with typical thromboangiitis obliterans.

The first patient (fig. 10, *A*) was a European man, 31 years of age, whose history had commenced six years previously with recurrent phlebitis and who developed typical intermittent claudication about two years later. He was seen for the first time four years after the onset of the phlebitis. At this time he had developed an ulcer on the first toe of his right foot. On clinical examination all pedal pulses were absent, the long and short saphenous veins showed definite but healed thrombosis, and there was a small ulcer on the great toe of the right foot. Both feet showed dusky red discoloration. Goldflam's sign was positive. The heart was normal on clinical examination and the blood pressure was 130/90. The fundi did not show any vascular

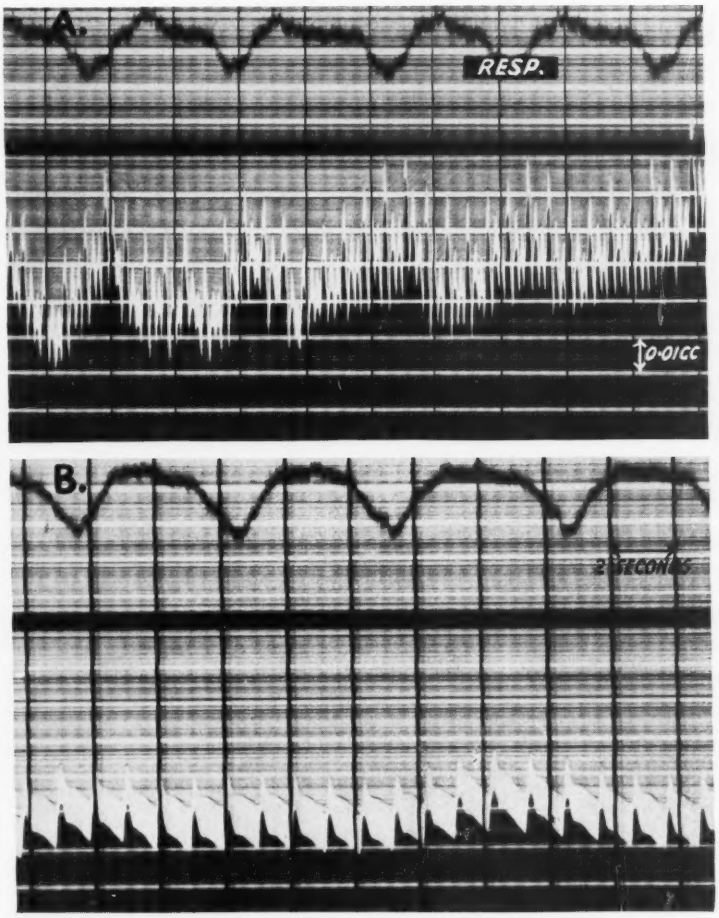

FIG. 7.—*A*. Pulse volume (first toe of right foot) as recorded in a patient with venous obstruction (reclining). *B*. Same limb, but elevated. Note difference in the shape of pulse volume. Tracings taken on different days.

changes. The nervous system and renal tract were normal. Special examination revealed complete block of the main arteries below the popliteal in both legs and the diagnosis of thromboangiitis obliterans was made.

The second patient was a young European man 27 years of age who had developed his first attack of phlebitis three years previous to examination. Ever since, he had had spells of thrombosis in one or other veins of any of the four extremities until two years before examination, when, for the first time, he developed intermittent claudication, numbness in both feet on walking, and symptoms of Raynaud's phenomenon in all extremities. He had been a heavy smoker always. He had not had enteric fever or any other illness. On examination, the heart was found to be normal, the blood pressure was 120/75, none of the peripheral pulses could be felt, and there were various cordlike segments of thrombosed veins in both legs. No trophic disturbances in the lower extremities were noted except for the absence of hair on both feet. The typical color changes were obtained, that is, pallor on elevation and dusky red in dependency. The central nervous system was normal, as were the fundi and urogenital tract. The diagnosis of thromboangiitis obliterans was made.

Figure 10, *A* and *C* illustrates the pulse volume of both these patients during rest in reclining posture. Again, the plethysmogram appears to record a fine tremor only, but on scrutiny a definite rhythm is noted, indicating that the pulse volume consists of three small but well developed waves. In the elevated position (fig. 10, *B* and *D*) the normal dicrotic pulse volume is recorded in both cases. It might be mentioned here, as it may be of significance, that in none of the patients was a monocrotic pulse recorded, as is often the case in the normal subject during elevation.

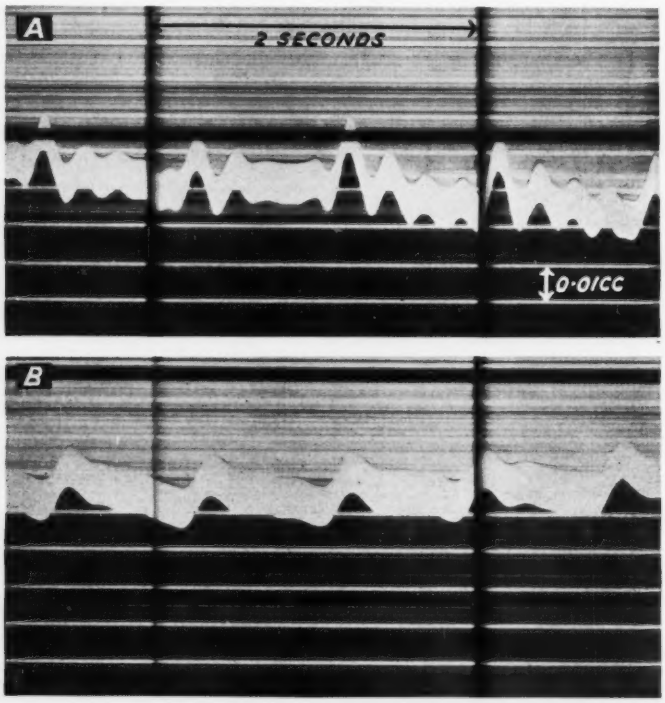

FIG. 8.—This record was made on the same patient as was the record shown in figure 7. The pulse volume was recorded at fast speed. *A*. Reclining; *B*. elevated.

These findings in a selected group of conditions confirm our contention that the changes in the shape of the pulse volume recorded are the result of interference with the venous drainage, which is the only common denominator in these cases.

Effect of Posture on Skin Temperature: There is no agreement in the literature as to the effect of changes in posture upon the peripheral circulation as judged by means of skin temperature measurements. Youmans, Ackeroyd, and Frank[24] found a decrease in the temperature of the toes of normal subjects in the upright posture, whereas Roth, Williams, and Sheard[25] reported the opposite: that under environmental temperatures ranging from 23 to 30 C., with the patient under basal conditions and free from sweating, the skin temperatures of the fingers and the toes decreased when the extremities were elevated and increased when

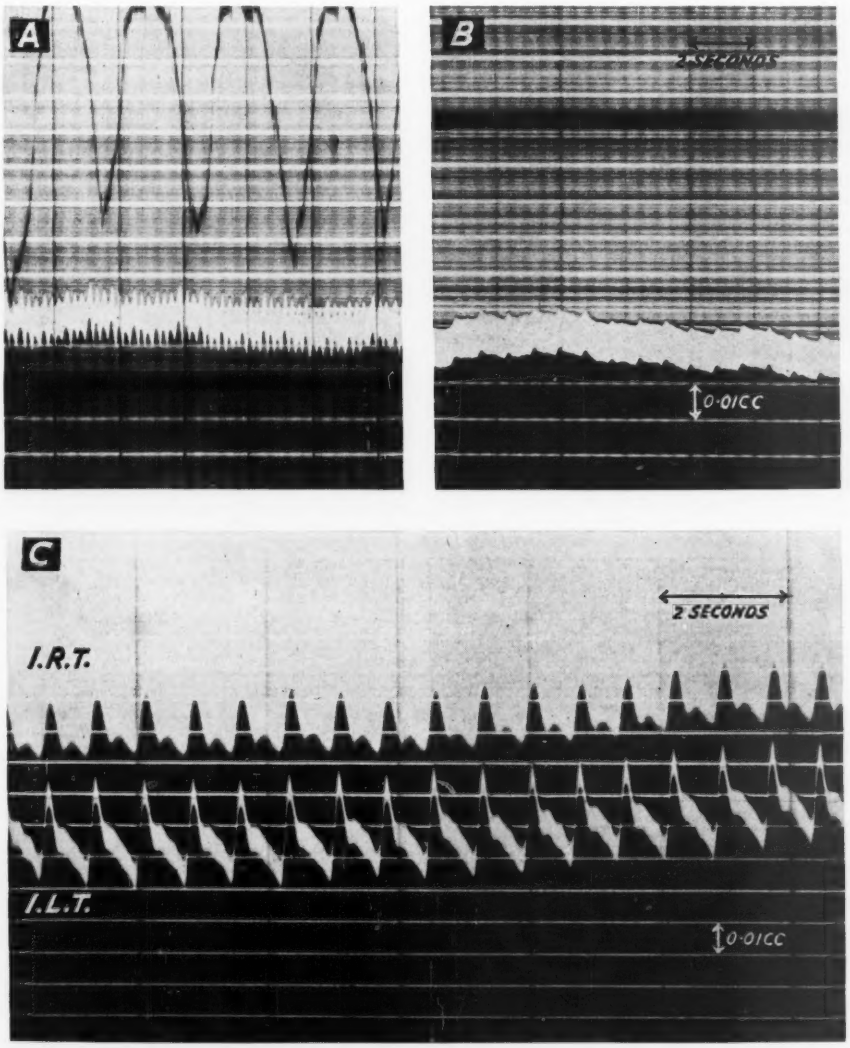

FIG. 9.—Pulse volume as recorded in a patient with thrombosis of the inferior vena cava. *A*. Reclining; *B*. elevated; *C*. pulse volume of first toe of left foot (upper tracing) and first toe of right foot (lower tracing) simultaneously recorded. Both in reclining position and during full dilatation. Patient had recent thrombosis of the left iliac vein. (Compare this figure with figure 4.)

they were pendent. The result was the same whether the changes in posture were obtained from changes in the posture of the body as a whole or from changes in the posture of the extremities themselves.

In this article we are not so much interested in the actual skin temperature during any particular posture but we wish to state that our findings confirm those of Roth, Williams, and Sheard.[25] Our interest centers around the response of the skin temperature, in limbs tested in different postures, to induced changes in vasomotor tone, as produced by body heating.

We have reported previously upon the effect

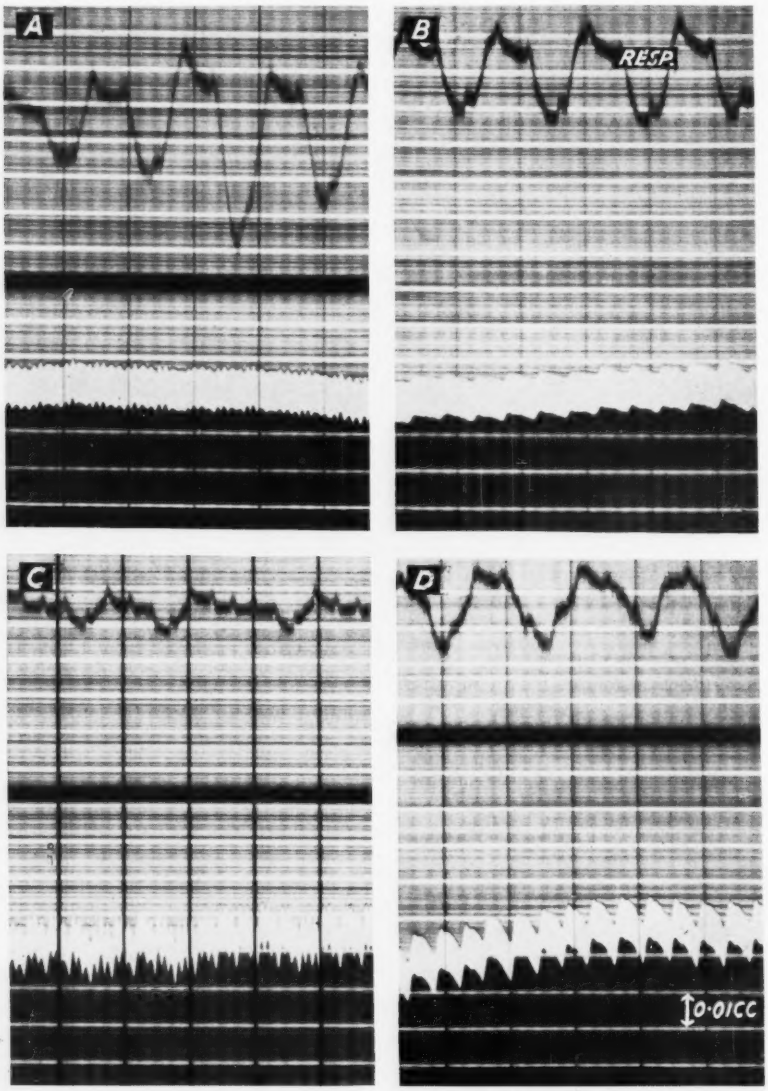

FIG. 10.—Plethysmogram in two typical cases of thromboangiitis obliterans. *A* and *C*. Reclining; *B* and *D*. elevated. Note that the appearance of the pulse in *A* and *C* is that recorded in the normal subject in the sitting or standing posture.

of body heating on the peripheral blood flow as judged by skin temperature and plethysmographic investigations. As the central vasomotor tone is released (fig. 11), the skin temperature rises within thirty minutes to the normal vasodilatation level (32 C.), the pulse

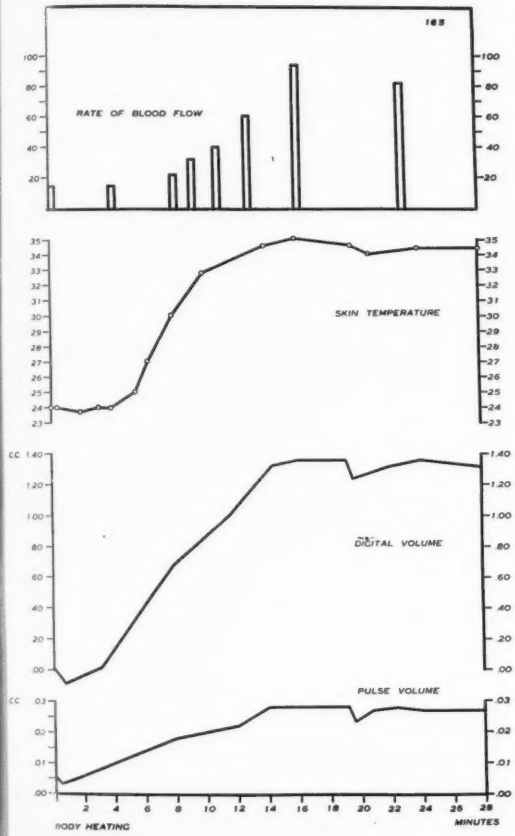

FIG. 11.—Graph prepared from continuous plethysmogram as obtained during body heating, demonstrating the normal response of the peripheral blood flow to the ablation of sympathetic tone. Rate of blood flow in cc. per minute for 100 cc. tissue, as calculated from venous congestion tests.

volume increases to at least 0.02 cc. and the digital volume increases depending upon the state of the vessels prior to body heating. At the same time the rate of blood flow per minute for 100 cc. of tissue reaches values between 80 and 100 cubic centimeters. All these findings refer to patients in the reclining position. Quite a different response may be recorded in a limb tested in a different posture. Figure 12 illustrates the point in question. The chart shows the response of the skin temperature to body heating in a patient in whom the right leg was kept hanging down while the left leg was elevated. As can be seen, there is a marked difference between the response of the skin temperature in the two legs. In the pendent limb the skin temperature rise, once initiated, is rapid and within twenty minutes reaches the normal vasodilatation level, registering a rise of 11 degrees C. In the elevated limb the rise

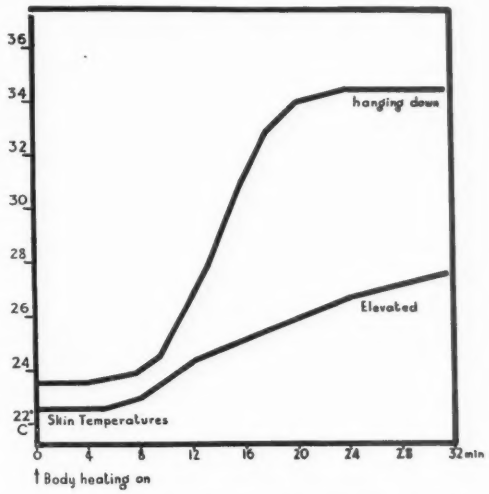

FIG. 12.—Effect of posture on the response of the skin temperature to the release of sympathetic tone as produced by body heating.

in skin temperature sets in after the same time interval but, in contrast to the pendent limb, 26 C. only is recorded after twenty minutes' body heating. After thirty minutes' body heating, when the skin temperature should have reached 32 C., it registers only 27 C. That this difference in the response of the skin temperature to body heating was not due to organic arterial disease but was caused only by the difference in posture could be demonstrated beyond doubt by reversing the posture of the two limbs, whereupon the same result is obtained; that is, the temperature of the now pendent limb reaches 32 C. easily, while the elevated limb shows hardly any skin temperature response. Furthermore, if at the end of the test the elevated limb is lowered, the skin

temperature rises rapidly and reaches the normal vasodilatation level within a few minutes.

These observations are of considerable importance since skin temperature readings are often employed for testing the patency of the peripheral vascular tree and a rise in skin temperature to 32 C. is regarded as the minimum vasodilatation level indicating normal circulation. The fallacy of this statement in other respects has been pointed out by us previously.[19,35] It was then demonstrated that a normal response of the skin temperature by no means precludes the possibility of organic arterial disease. The present investigations demonstrate that even slight changes in posture affect the speed and the ultimate level of the skin temperature rise accompanying reflex vasodilatation. In the elevated limb the skin temperature response is diminished and retarded and may never reach the normal vasodilatation level, and this in a limb which is known to be normal. In pendent posture, however, the normal vasodilatation level is reached easily within thirty minutes, usually much earlier. By elevating the limb the skin temperature in a normal subject can be induced to simulate the response characteristic of organic occlusion. The reverse holds good, too, since in a leg with advanced occlusion the skin temperature can be made to reach the normal vasodilatation level by adopting a more dependent posture.

Recording the skin temperature only, one gets the impression that with elevation of the extremities body heating does not, or only partially, results in reflex dilatation. Indeed, this was the conclusion at which Uprus, Gaylor, and Carmichael[26] arrived. On consulting the plethysmogram, however, one realizes that this cannot be correct (fig. 13). The pulse volume, independent of the posture and in contrast to the skin temperature, reaches the vasodilatation level easily within thirty minutes. Actually, the pulse volume reaches considerably higher values in the elevated limb (figs. 13 and 14). One is confronted, therefore, with the apparently paradoxic situation that in elevated limbs after thirty minutes' body heating the skin temperature is such as would indicate marked interference with the peripheral circulation, while the pulse volume actually is well above the normal minimum vasodilatation level, giving proof of the fact that the arterial circulation is entirely adequate. The plethysmographic findings, therefore, lend

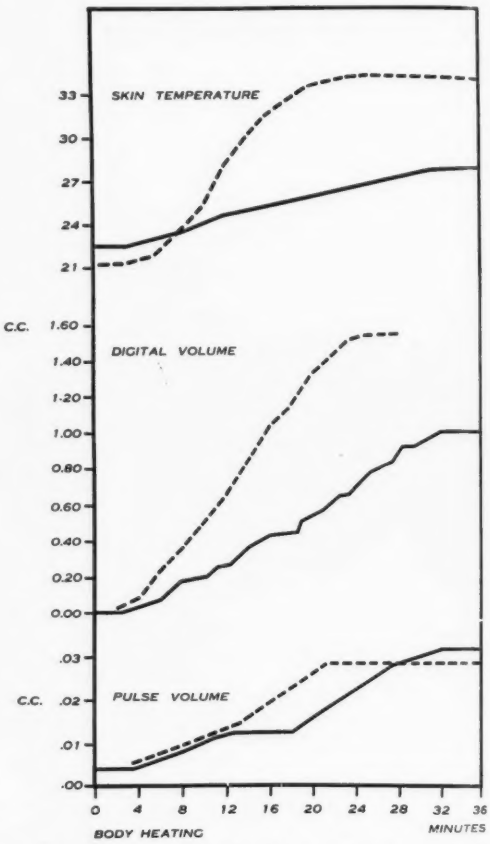

FIG. 13.—The effect of posture on the response of the peripheral circulation to the release of sympathetic tone as produced by body heating. Interrupted lines represent normal response with the patient in reclining position; uninterrupted lines, the response with limbs elevated. Note the difference in skin temperature and higher pulse volume in the elevated limb during full dilatation.

no support to the conclusions drawn by Uprus and co-workers[26] that the diminished response in the skin temperature is due to incomplete reflex vasodilatation, but prove that the arterial tree is dilating in the normal fashion. It is the difference in the venous drainage which brings about the diminished rise in skin tem-

perature to body heating. No better example could be found to demonstrate the caution which has to be exercised when translating skin temperature measurements into terms of arterial blood flow. The skin temperature is a function of the venous drainage to a degree hitherto unrecognized. The clinical implications of this observation in such conditions as iliac thrombosis and arteriovenous fistula are obvious and will be dealt with separately. It is essential to record the posture whenever skin temperature readings are taken and no doubt some observations reported in the literature lose much of their significance in the light of these data.

From these observations it must be clear that any clinical condition which interferes with the venous return from the extremities must of necessity produce an increase in skin temperature and such a limb should warm more quickly on body heating. Indeed, in contrast to the writings of some authors,[27, 23] we have found, in keeping with the findings which have been stated, that in the vast majority of cases of unilateral venous thrombosis the affected limb is warmer and not colder than the normal limb. Actually, this has been observed by many of our patients themselves. Not only is the actual skin temperature increased, but it has been found that on body heating the skin temperature of the affected limb rises much more quickly than that of the normal limb, and the ultimate skin temperature of the affected limb often is higher than in the normal limb.

These findings are not merely of academic interest, as the following case history demonstrates.

A Jewish man, aged 38 years, who had symptoms suggestive of intermittent claudication in the left leg, was referred to us. The previous investigator had found a definite difference in the response of the skin temperature of the two lower limbs to reflex vasodilatation. The left limb warmed up more slowly than the right one, although the skin temperature eventually reached the normal vasodilatation level in both. Clinically, there was a difference in the strength of the pedal pulses, but there were no signs of arterial disease. On the strength of the difference in the skin temperature response to reflex vasodilatation, the previous investigator diagnosed early thromboangiitis obliterans in the left leg. When we examined the patient the findings of the previous examiner could be confirmed: the skin temperatures increased more rapidly in the right leg than in the left on body warming, and there was a difference in the strength of the arterial pulses in the two limbs. However, the arterial circulation in both legs was normal, as judged by plethysmographic examination. When it could be proved that there was interference with the venous drainage, it was obvious that it was not the left limb which showed a diminished response to reflex vasodilatation, but that it was the right limb which warmed up more quickly. When this patient was re-examined four years later, the plethysmogram still gave normal values in both limbs. There were no signs of any arterial disease. The difference in the pedal pulses was explained as an anatomic abnormality. We do

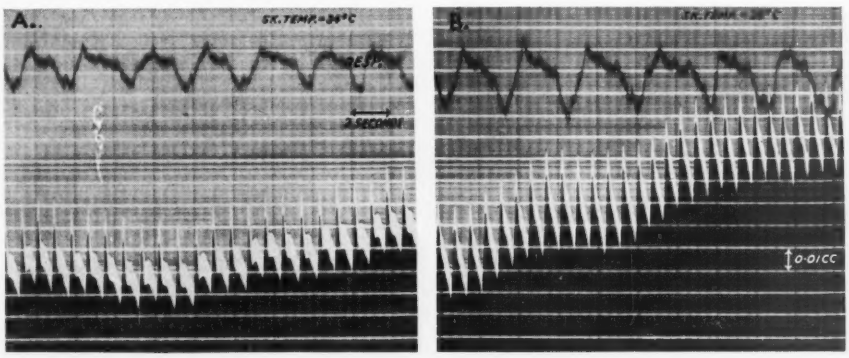

FIG. 14.—Pulse volume of same patient whose record is shown in Fig. 13. This graph demonstrates the higher pulse volume during full dilatation in the elevated limb, despite the lower skin temperature. In *A*, pulse volume is ±0.028 cc. (reclining position); in *B*, pulse volume is ±0.032 cc. (elevated position).

know that in 12 to 14 per cent of normal subjects the arteria dorsalis pedis may be diminished or absent, while the posterior tibial may be absent in about 2 to 5 per cent of cases.[29, 30]

Discussion

Before entering into any discussion of the results, a decision must be made as to whether the changes in the peripheral circulation observed with alterations in posture as described in this article are caused by differences in hydrostatic pressure and venous drainage or have to be attributed to sympathetic reflex phenomena. Since the changes could also be recorded in the sympathectomized limb, it appears that a central or spinal vasomotor reflex can be excluded and that the observed reactions must be explained in terms of alterations in the venous drainage and hydrostatic pressure.*

In the past the results of both skin temperature readings and plethysmography have been interpreted solely in terms of function and patency of the *arterial* tree. The influence which may be exercised by changes in venous drainage on the skin temperature and the plethysmographic appearances have hardly been considered. One method by which the venous drainage in the normal person may be altered is by changing the posture. Few investigators, however, have examined the effect of posture on skin temperature and none its effect on the plethysmographic appearances. Such skin temperature studies as are available are contradictory. Roth, Williams, and Sheard[25] found that elevation will decrease, and dependency increase the skin temperature, while Youmans, Ackeroyd, and Frank[24] reported contrary results. Our own investigations are in full agreement with those of Roth and co-workers. However, we were not so much concerned with the actual skin temperature at different postures, as with the effect of posture upon the response of the skin temperature to body heating. The latter is rather important since body heating is generally used as a test for assessing the state of the peripheral circulation. Gibbon and Landis,[31, 32] who popularized this test, were of the opinion that a rise in skin temperature to 32 C. within thirty to thirty-five minutes "definitely excludes the possibility of obliterative structural disease of the arteries," a criterion which is generally accepted. Jahsman and Durham[33] state that such a response excludes the possibility of obliterating structural disease of the artery. However, in a previous paper[19] we brought forward evidence that skin temperatures may still give "normal" values when the blood flow is as much as 50 per cent below normal, as judged by plethysmography. The correctness of the plethysmographic readings was proved subsequently by postmortem examinations.

In the present paper it is demonstrated that even if the blood flow, as judged by plethysmography, is normal, the criteria of Gibbon and Landis are still not acceptable without further qualification. By merely elevating a normal limb the response of the skin temperature can be modified to such an extent that with body heating it may reach only 27 or 28 C. during the thirty minutes normally allowed to reach the vasodilatation level. The same limb in a horizontal or slightly pendent posture will easily give the "normal" response, that is, reach 32 C. Uprus, Gaylor, and Carmichael[26] had already observed this difference and they concluded that, in the elevated limb, body heating is not capable of overcoming vasoconstrictor tone. By investigating this question with our plethysmographic method, we could clearly demonstrate that, despite this difference in skin temperature, there is no difference between the blood flow in the elevated and the pendent limb and that the vasoconstrictor tone is released simultaneously in both, irrespective of the posture. The moment the necessity of the body to dissipate heat arises, vasomotor tone diminishes, whether the limb is elevated or not. Indeed, it could be demonstrated that after thirty minutes' body heating the pulse volume is actually larger during elevation than during dependency, and this at a time when the skin temperature has failed to reach the normal vasodilatation level. There may be a deficit of up to 8 degrees C. Hence, the failure of the skin temperature to rise cannot be due to a

* However, it is necessary to state clearly that this does not imply that differences in vasomotor tone between the upper and lower extremities which we explain as being due to differences in posture are not due to central sympathetic activity.

failure to overcome vasoconstrictor tone in the elevated position. The plethysmographic investigations suggest very strongly that such differences as are observed in the skin temperature are due to changes in the hemodynamics in general and changes in the venous drainage in particular, as produced by changes in posture.

During elevation there occurs a fall in venous pressure, an emptying of the larger veins, and a drainage of Wollheim's subpapillary venous plexus. The blood returns hastily through collapsed veins. Our investigations therefore suggest strongly that the skin temperature is to a large degree a function of the venous drainage. The fact that the skin temperature in the elevated limb does not rise with reflex body heating to the normal vasodilatation level is due, then, to facilitation of the venous drainage during elevation. It may be concluded that it is not only the amount of blood but also the time which the blood takes to flow through the subpapillary venous plexus and through the small veins which determines the ultimate skin temperature. If the blood is rushing through these channels, as in the elevated limb, then there is no time for the blood to give off heat and transmit its temperature to the surrounding tissue and the skin temperature will be relatively low. The contrary occurs in the pendent limb where the slightest release of the arterial tone accompanied by the pooling of blood causes a rapid increase in skin temperature. On body heating, therefore, the skin temperature in a pendent limb rises rapidly and reaches the normal vasodilatation level before there occurs full vasodilatation of the vessels. While in the *elevated* position the skin temperature of the limb will not reach the normal vasodilatation level within thirty minutes of body heating in a person with normal arteries; in the *pendent* limb the skin temperature easily reaches the normal vasodilatation level even if there is already advanced organic arterial interference. Posture, therefore, is an important factor in determining the actual skin temperature and the results of the present study demonstrate clearly the limitations of skin temperature readings in assessing the peripheral circulation. Whenever skin temperature readings are reported the posture should be stated, otherwise unreliable or incorrect conclusions will be drawn from such investigations.

In the pendent posture, with the arteries moderately dilated, the skin temperature of the feet would always be in the neighborhood of 34 to 35 C.; dissipation of heat would therefore be maximal. Obviously this is not in the interests of an economical body temperature regulation. To overcome this effect of the upright posture, therefore, a high vasomotor tone in the lower extremities develops to reduce blood flow and heat loss. The high vasomotor tone of the lower extremities therefore is explained as the result of man's assumption of the upright posture which, by virture of its hemodynamic effect in general and interference with the venous drainage in particular, militates against the use of the lower extremities in body temperature regulation. As we have pointed out previously,[19] under ordinary conditions the blood flow through the lower extremities is mobilized for body temperature regulation only when the capacity of the upper extremities has been fully exhausted.

These findings have a definite bearing on the understanding of the clinical picture of such conditions as varicose veins, venous thrombosis, scleroderma, and arteriovenous fistula, and on the management of the edematous ischemic limb. There is always some hesitation in elevating the edematous and ischemic limb to promote increase in lymphatic drainage because with elevation there occurs a decrease in skin temperature. The results of the present study indicate that this does not necessarily mean that there is a diminution in arterial blood flow. The contention of Bazett,[34] that in the elevated limb the reduced bore of the collapsed veins increases the resistance to the capillary blood flow, is not borne out by our results since the pulse volume in the plethysmogram is actually higher in the elevated than in the horizontal or dependent limb. Accordingly, one need not hesitate to elevate the edematous limb to increase the flow of lymph, decrease interstitial pressure on the capillaries, and promote capillary blood flow.

It appears, too, that at least part of the different response of the lower extremities to

sympathectomy can be attributed to the difference in posture. Sympathectomy abolishes the higher vasomotor tone normally observed in the lower extremities. The veins being sympathectomized as well as the arteries, relaxation occurs in both, with but one difference; that the veins with their poor muscular coat do not reacquire that degree of tone seen in the arteries some time after sympathectomy. Hence, following sympathectomy there occurs pooling of blood in the veins and slowing of venous return which, apart from any increase in the arterial circulation, will, as we have seen, lead of its own accord to an increase in skin temperature. Normally, this pooling of blood does not assume pathologic dimensions since it is partly counteracted by the muscular activity. This can be proved by investigating the effect of sympathectomy in subjects in whom the venous return is not assisted by muscular activity. Pooling of blood becomes marked and of pathologic significance. This we have observed in a number of patients with poliomyelitis in whom there was almost complete paralysis and atrophy of the muscles of the lower leg with marked vasospastic disturbances. Such patients develop marked edema following sympathectomy because the pooling of blood is not counteracted by the muscular pump. Therefore we have discontinued performing sympathectomy in the paralyzed limb with marked atrophy of the muscles, even if it can be demonstrated that the circulatory disturbances are entirely vasospastic in nature.

In the past we always interpreted the height of the pulse volume in the digital plethysmogram in terms of patency of the arterial tree. The present account demonstrates the profound effects of posture on both the height and the shape of the pulse volume. The knowledge of these changes is of practical interest. It has been noted that in many cases of thromboangiitis obliterans, in some cases of thrombophlebitis, and in some cases of thrombosis of the inferior vena cava, the normal dicrotic pulse shape is replaced by three or four equally high elevations, when tested with the subject in the usual reclining posture. In the normal person a similar pattern may be produced if if the test is made with the individual in the erect or sitting posture. This suggests strongly that it is the changes in the hemodynamics in general and interference with the venous drainage in particular which account for the changes observed. Knowing that venous thrombosis is characteristic in thromboangiitis obliterans, it appears justified in the light of these observations to interpret such changes in the shape of the pulse volume in these cases as the result of venous involvement. It may thus be possible in a case of suspected thromboangiitis obliterans, in which no signs or symptoms of venous involvement are manifest, to determine whether venous thrombosis has occurred to any extent, thus adding considerable weight to the presumptive diagnosis in a doubtful case. Such observations would also be particularly important in patients in their forties in whom the differential diagnosis between arteriosclerosis and thromboangiitis obliterans may present considerable difficulties. However, further studies will be necessary.

The observed postural changes in the plethysmographic appearances in general and of the pulse volume in particular make it obligatory, too, that the posture always be indicated whenever the plethysmogram is consulted. It is therefore important to standardize the posture in which tests are carried out in order to get comparable results. In the past we have carried out all our tests in the position indicated in figure 1, using the couch and accessories developed in our laboratories. This has proved most convenient in many thousands of tests during the last ten years. It is likely that, with the development of portable plethysmographs,[20,35] plethysmography may be more commonly employed for assessing the peripheral circulation, as its merits deserve. We would suggest, therefore, that investigators adopt the posture indicated as standard. A similar plea may be made with regard to skin temperature readings, as is evident from the investigations reported in this paper.

The suggested position has the advantage that patients with cardiac decompensation, in whom one is very often called upon to investigate the peripheral circulation, can easily be tested. In the horizontal posture difficulties

would arise in patients with any degree of orthopnea.

There is no doubt that any investigation of the peripheral circulation without due respect to posture loses much of its significance in view of the present investigations, and many of the controversial results may be explained on this basis.

The present investigations may be of some significance, too, in evaluating such therapeutic measures as make use of changes in posture, such as vascular exercises or Saunder's oscillating bed. Further investigations with our method, as outlined herein, should furnish valuable results as to the efficacy of such methods in improving the peripheral circulation.

Summary and Conclusions

1. The effect of posture on the peripheral blood flow has been investigated by means of the Goetz digital plethysmograph and skin temperature readings.

2. It is demonstrated that even slight changes in posture have marked effect on the plethysmographic appearances. Both the height and the shape of the pulse volume are affected.

3. With the subject in the erect posture the height of the pulse volume is only a fraction of that recorded in the elevated limb.

4. The changes in the shape of the pulse volume with changes in posture are marked. In the elevated limb the pulse volume tends to be monocrotic. With the subject in the erect posture the dicrotic wave is pronounced and is usually followed by one or two more waves. The notch between the main elevation and the dicrotic wave reaches the base line.

5. With the limb in the dependent posture all changes in digital volume, both spontaneous and those induced by extrinsic and intrinsic stimuli, are greatly diminished. In the elevated position they are very much pronounced.

6. The changes described are recorded irrespective of whether the posture of the limb only or that of the whole body is altered.

7. The changes in the plethysmographic appearances resulting from changes in posture are recorded in the sympathectomized limb and therefore are not due to changes in the vasomotor tone but to alterations in the hemodynamics and venous drainage.

8. In patients with obstruction of the venous return and in some patients with thromboangiitis obliterans, the pulse volume with the subject in the reclining posture assumes the shape normally seen only in the dependent limb. Conversely, interference with the venous return may be suspected if the pulse volume tested when the individual is reclining shows the features normally seen only in the erect position. The clinical importance of this finding in determining the patency of venous circulation is stressed.

9. The effect of changes in posture on the skin temperature is discussed. It is demonstrated that in the elevated limb the skin temperature does not reach the normal vasodilatation level on body heating. This is not due (as had been thought by previous authors) to a failure in the release of sympathetic tone. Plethysmography shows that in the elevated posture the vessels dilate in the usual manner. The pulse volume records normal values, despite the lower skin temperature. This provides an excellent example of the superiority of digital plethysmography over skin temperature readings in assessing the state of the peripheral circulation.

10. It is demonstrated that this diminished response in skin temperature is due to the change in venous drainage. The state of the venous drainage, therefore, is almost as important a factor in determining the skin temperature as is the arterial supply.

11. The clinical importance of these findings is discussed in relation to the better effect of sympathectomy in the lower extremities and in relation to the indications for sympathectomy in patients with marked wasting of muscles (poliomyelitis).

12. In the past the results of both skin temperature readings and plethysmography have been interpreted solely in terms of function and patency of the arterial tree. This concept has to be revised. The study of the effect of changes in posture on the peripheral circulation demonstrates clearly that the venous limb of the vascular tree plays a part unrecognized hitherto.

ACKNOWLEDGMENTS

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Determination of Blood Volume in the Heart and Lungs and the Cardiac Output through the Injection of Radiophosphorus

By GUSTAV NYLIN, M.D., AND HJÖRDIS CELANDER, M.Sc.

The dilution curve of the specific activity of the erythrocytes in the arterial blood after intravenous injection of labeled erythrocytes with P^{32} has been treated mathematically. It is possible with the help of the dilution curve to calculate the minute volume of the heart and the thoracic pool (the residual blood of the heart + the blood content of the lungs). The values of the thoracic pool amount to about 30 per cent of the total circulatory blood-volume.

THIS REPORT describes a method for the estimation of the cardiac output and the blood volume of the heart and lungs (referred to as the Pool Volume) by the use of red cells labeled with radioactive phosphorus (P^{32}). A theoretic analysis of the experimentally obtained data has led to the development of a formula for the cardiac output exhibiting a certain similarity to earlier formulas reported by Kinsman, Moore and Hamilton.[6]

METHOD

A sample of venous blood, taken from the patient to be studied, is incubated with radiophosphorus in the form of sodium acid phosphate. The red blood corpuscles in the sample are consequently labeled with P^{32} according to the method of Hevesy and associates.[1–3] A given quantity of the labeled material is reinjected into the antecubital vein. Arterial blood is then serially sampled at short intervals. The concentration of radiophosphorus in the extracted samples having been ascertained, a curve (referred to as the Dilution Curve) may be plotted of the arterial concentration, c, as a function of time. The characteristics of such dilution curves under normal and abnormal circumstances have been reported in more detail previously.[4–5] Such a dilution curve is illustrated in figure 1.

Examination of this figure will show: (1) That maximum concentration at Point A of the curve is derived from the concentration of the injected indicator which for the first time passes the testing point (here called the primarily circulating indicator). (2) That maximum concentration at Point L is derived partly from the concentration of the indicator passing through the body for the second time (after having followed the shortest possible course through the body) and partly from the primarily circulating indicator. (3) That the recirculation at Point B of the curve sets in before the whole volume of indicator has passed the testing point for the first time. At Point L of the curve the concentration is derived partly from the respective concentrations of the recirculating indicator (E) and the primarily circulating indicator (F).

Because of the impossibility of distinguishing E from F by direct determination, a method must be developed to do this mathematically. That is to say, one must know the equation of the curve GB to be able to extrapolate the curve beyond the Point B.

In order to examine whether the curve has an exponential form, the logarithm of the concentration ($log\ c$) has been drawn as a function of time (Fig. 2). It then appears that the curve segment GB has the character of a straight line with the equation*

$$log\ c = -\lambda t + \alpha \qquad (1)$$

where $-\lambda$ = the slope of the line, t = the time, c = the concentration, α = a constant. It therefore seems practically justifiable to give the equation of this segment of the curve as:

$$c = c' \cdot e^{-\lambda t} \qquad (2)$$

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* A glossary of symbols used in text, figures and equations is given in the Appendix, page 83.

where e = the base of the natural log. system (appr. = 2.72), and c' = a constant.

If the perpendicular axis of a diagram like that of figure 2 is logarithmic, it seems rather

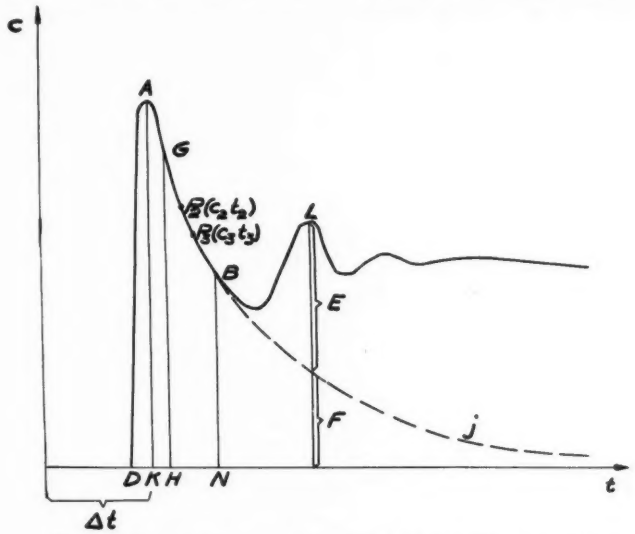

FIG. 1.—GENERAL DILUTION CURVES (see Appendix for symbols).

probable that part of the curve thus obtained will assume, more or less, the character of a straight line even in those cases where the original curve noticeably diverges from the exponential form.

It thus seems justifiable to try to analyze the mixing conditions from a more theoretic point of view. We will therefore examine the mixing process in a system of receptacles through which a fluid is allowed to flow. A quantity of indicator is then injected at Point A_1 (fig. 3). This system of receptacles has been designed so as to resemble the circulatory system of heart and lungs.

The quantity of indicator which per unit time passes Point B_1 of the system of receptacles is a function of time $[=f_1(t)]$, as is also the quantity of indicator which per unit time passes $C_1[=f_2(t)]$.

$$\text{Thus, } \frac{dm}{dt} = f_1(t) - f_2(t) \qquad (3)$$

where m = the amount of indicator in the receptacles.

When the greater part of the indicator has passed the testing point, D_1 (fig. 3), and before the recirculation has set in, it may, with fair approximation, be assumed that $f_1(t) = 0$, as practically all the indicator must then have

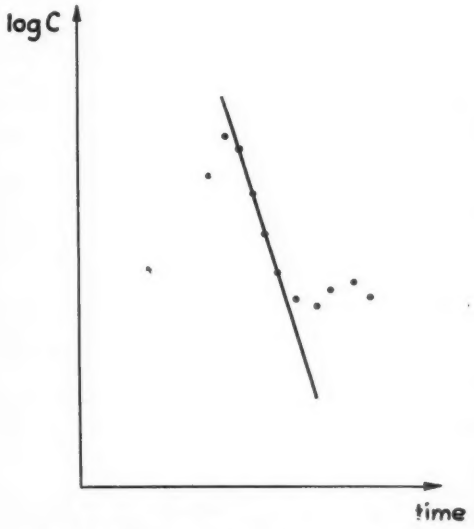

FIG. 2.—DILUTION CURVE ON A LOGARITHMIC SCALE. Straight line represents segment GB produced.

passed Point B_1. Further,

$$f_2(t) = Xc_1'$$

where c_1' = concentration at Point C_1 in the receptacles (fig. 3), and X = rate of flow (in liters per minute)

$$\text{Thus, } \frac{dm}{dt} = -Xc_1'.$$

The rate of flow through the receptacles is constant. The mean concentration c_m in the receptacles (excluding the recirculating indicator) is necessarily smaller than the concentration c_1'. Therefore it may be assumed that

$$c_1' = Sc_m$$

where S is a factor greater than 1.

$$\text{Thus, } \frac{dm}{dt} = -XSc_m = -X \cdot S \cdot \frac{m}{V} \qquad (4)$$

where V = volume of the receptacles in liters. Integration of Equation 4 gives

$$m = m_0\, e^{-(XS/V)\,t} \qquad (5)$$

where m_0 = the integration constant. Hence from Equation 5 we get by differentiation:

$$\frac{dm}{dt} = -m_0 \cdot \frac{XS}{V} \cdot e^{-(XS/V)\,t} \qquad (6)$$

In this equation every symbol refers to the conditions in the receptacles. Equation 6 may be compared with Equation 2 which was derived from practical determinations.

Equation 2 gives the concentration at a point corresponding to Point D_1 in Fig. 3. Through multiplication of Equation 2 by the cardiac output, X_1, we get

$$X_1c = X_1 \cdot c' \cdot e^{-\lambda t}$$

but $X_1c = -\frac{dm_1}{dt}$ where $\frac{dm_1}{dt}$ = the amount of indicator passing the testing point per unit time.

$$\therefore \frac{dm_1}{dt} = -X_1 \cdot c' \cdot e^{-\lambda t} \qquad (7)$$

A comparison between the practically obtained Equation 7 and the mathematically obtained Equation 6 shows that both are of exponential form. Therefore, the circulatory conditions in the body may be expressed in the following form:

$$\frac{dm_1}{dt} = -X_1c'e^{-(X_1S_1/V_p)t} \qquad (8)$$

where V_p = the pool volume.

S_1 = a factor > 1, illustrating the ratio of the concentration at the test point to the mean concentration of the primarily circulating indicator in heart and lungs during the time interval HN (fig. 1).

As further support for the correctness of Equations 7 and 8 the works of Kinsman, Moore, and Hamilton,[6] who reached the same result, may be cited. These workers built up a mechanical system of the type shown in figure 3, which reproduced as closely as possible

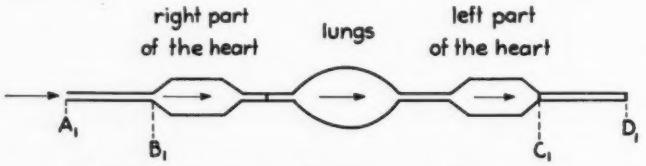

FIG. 3.—EQUIVALENT HYDRODYNAMIC SYSTEM.

the actual conditions existing in the heart and lungs. The indicator injected at a point corresponding to A_1 in figure 3 was conveyed by means of a pumping system through the receptacles and past the testing point. By an arrangement such as this, disturbances from the recirculating indicator may be avoided and the dilution curve may be followed during a considerably longer period than is possible in the human body.

CALCULATION OF CARDIAC OUTPUT

From a curve of the type shown in figure 1 the cardiac output may be estimated, since there are two expressions for the total quantity of indicator:

$$h_iv_ic_i = \int_0^\infty cX_1h\,dt$$

where h_i = the hematocrit of the injected sample, v_i = volume of injected labeled blood, c_i = concentration of indicator of the injected

sample, h = the hematocrit of the circulating blood.

Since it may be assumed that the cardiac output and the hematocrit of the circulating blood are constant under constant conditions, we may write

$$h_i v_i c_i = X_1 h \int_0^\infty c\,dt$$

$$\text{Thus, } X_1 = \frac{h_i \cdot v_i \cdot c_i}{h \cdot \int_0^\infty c \cdot dt} \tag{9}$$

where $\int_0^\infty c\,dt$ = the area limited by the curve $DAGBJ$ (fig. 1) and the time-axis. Of this area the part $DAGH$ ($= R$) must be determined graphically. The area below GBJ is determined as follows:

$$\int_H^\infty c' e^{-\lambda t}\,dt$$

$$\text{Therefore } X_1 = \frac{v_i c_i}{R + \int_H^\infty c' e^{-\lambda t}\,dt} \cdot \frac{h_i}{h} \tag{10}$$

All time units expressed in minutes, all volumes in liters. c' and λ are constants to be determined from the curve segment GB. Suppose we have two points on GB: P_2 ($c_2 t_2$) and $P_3(c_3 t_3)$.

$$\text{Then } \begin{cases} c_2 = c'\, e^{-\lambda t_2} \\ c_3 = c'\, e^{-\lambda t_3} \end{cases}$$

$$\text{Thus, } \begin{cases} \lambda = \dfrac{\ln c_2 - \ln c_3}{t_3 - t_2} & (11) \\ c_2 = c' e^{-\lambda t_2} & (12) \end{cases}$$

Here only λ and c' are unknown.

Determination of the Blood Volume of the Heart and Lungs (V_p).

The time Δt (fig. 1) is the average time taken for the blood to travel from the point of injection to the testing point, that is, from the vein of one arm to the artery of the other. $X_1 \cdot \Delta t$ = the quantity of blood found in the heart, lungs, arteries and veins from the heart to the elbow and to points equidistant to the elbow. The blood in the coronary arteries and veins is not included in the volume $X_1 \cdot \Delta t$.

A comparison of Equations 7 and 8 shows that

$$\frac{X_1 S_1}{V_p} = \lambda$$

$$\therefore V_p = S_1 \cdot \frac{X_1}{\lambda}$$

$$\text{Thus, } V_p > \frac{X_1}{\lambda}.$$

$$\text{Set: } \frac{X_1}{\lambda} = V_2$$

We have accordingly here established an upper limit $V_1 = X_1 \cdot \Delta t$ and a lower limit $V_2 = \frac{X_1}{\lambda}$.

The time Δt is usually considerably greater than the transit time through heart and lungs; in other words $X_1 \Delta t$ is considerably greater than V_p. On the other hand,

$$V_p = S_1 \cdot \frac{X_1}{\lambda}$$

where S_1 is the ratio between the concentration at the testing point and the mean concentration of the primarily circulating indicator in heart and lungs. Here S_1 is normally appreciably greater than 1, and hence V_p is much greater than $\frac{X_1}{\lambda}$.

If one therefore puts $V_0 = \frac{V_1 + V_2}{2}$ the divergence of the mean value V_0 from the real value V_p will be considerably lower than $V_0 - V_1$, respectively $V_0 - V_2$.

The total blood volume of the body has been determined from the horizontal part of the curve. This determination was made twenty to sixty minutes after injection. Due to the fact that after this period of time the blood has become homogenously mixed with the indicator, the following equation has been obtained:

$$V_t = \frac{c_i \cdot v_i \cdot h_i}{c_h \cdot h}$$

where V_t = total blood volume of the body, and c_h = concentration of the samples taken between twenty and sixty minutes after injection.

In some cases there has been difficulty in determining the injected amount V_i. In these cases a constant K_1 has been introduced for the total blood volume; and the amounts of

X_1, V_1, and V_2 have been calculated as percentages of the total volume, K_1.

Results

The results are epitomized in tables 1 to 4 (see also figs. 4 to 7).

Table 1.—*Cardiac Output, Pool Volume of the Chest and Total Circulatory Blood Volume in Normal Subjects and in Patients with Heart Disease.*

Case	Cardiac output (X_1) (liters)	Pool Volume: Upper limit ($V_1 = X_1\Delta t$) (liters)	Pool Volume: Lower limit ($V_2 = \frac{X_1}{\lambda}$) (liters)	Pool Volume: Mean value ($V_0 = \frac{V_1 + V_2}{2}$) (liters)	Pool Volume: % of total blood volume	Total blood volume in the body (V_k) (liters)
1	3.7	2.9	2.8	2.85	33	8.6
2	4.4	2.2	1.3	1.75	32	5.5
3	5.0	1.9	1.2	1.55	34	4.5
4	2.3	1.3	1.1	1.20	29	4.2
5	1.35K	0.45K	0.15K	0.30K	30	K
6	1.60K	0.41K	0.29K	0.35K	35	K
7	0.79K	0.42K	0.21K	0.32K	32	K
8	1.10K	0.43K	0.17K	0.30K	30	K

Table 2.—*Roentgenologic Heart Volume and Hematocrit in Normal Subjects and in Patients with Heart Disease (Same Cases as in Table 1).*

Case	Diagnosis	Roentgenologic heart volume (liters)	Body weight (Kg.)	Hematocrit (%)
1	mitral stenosis	3.1	70	44.5
2	" "	1.8	72	36.0
3	aortic insufficiency	0.85	69	43.0
4	orthostatic hypotension	—	69	50.0
5	normal case	0.60	66	—
6	" "	—	—	43.0
7	cardiosclerosis	1.35	50	51.5
8	aortic insufficiency	1.72	45	39.0

As seen from table 2, tests have been made on normal as well as pathologic cases. As a means of comparison, heart volumes determined through roentgen rays, according to the method of Liljestrand, Lysholm, Nylin and Zachrisson,[7] have been given.

$$\text{Heart volume} = K_2 \cdot \frac{4}{3}\pi \cdot \frac{a_2 \cdot a_3 \cdot a_4}{8} \qquad (13)$$

where a_2 = the largest diameter, a_3 and a_4 = the largest diameters perpendicular to a_2 and to each other, K_2 = a proportionality constant.

The heart volumes thus obtained consist not only of the blood volume of the heart but also of the muscle tissues of the heart. In the cases where the heart volume determined by x-ray gives a higher value than the blood volume in heart and lungs, these values do not contradict each other.

As appears from table 1, the blood volume

Table 3.—*Specific Activity of Red Cells from Arterial Blood after Intravenous Injection of Labeled Red Cells in a Normal Case (Case 5 in Tables 1 and 2 and Fig. 5).*

Time after injection (seconds)	Concentration impulses / gram min.	Time after injection (seconds)	Concentration impulses / gram min.
5	—	39	118
7	—	41	122
9	—	43	123
11	—	45	113
13	56	47	100
15	173	49	103
17	226	51	106
19	260	53	99
21	250	55	93
23	248	57	95
25	189	60	98
27	148	120	104
29	109	180	96
31	103	240	107
33	52	300	97
35	122	600	86
37	119	900	88

Table 4.—*Specific Activity of Red Cells from Arterial Blood after Intravenous Injection of Labeled Red Cells in a Case of Heart Dilatation (Case 1 in Tables 1 and 2 and Fig. 7).*

Time after injection (seconds)	Concentration impulses / gram min.	Time after injection (seconds)	Concentration impulses / gram min.
0–30	—	100	238
35	105	105	221
40	348	110	220
45	458	115	208
50	435	120	218
55	392	180	199
60	337	300	204
65	315	420	169
70	283	600	178
77	262	900	178
85	243	1800	173
93	230		

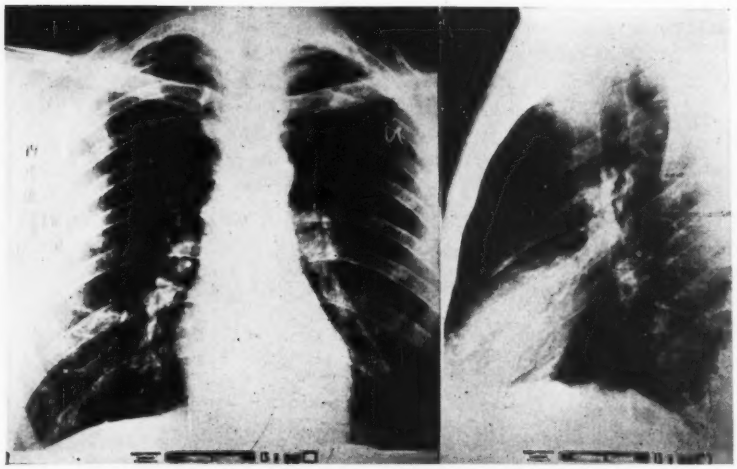

FIG. 4.—X-RAY OF THE HEART, NORMAL SUBJECT (Case 5).

of heart and lungs seems to vary from 29 to 35 per cent of the total blood volume.

There is a certain correlation between the roentgenologic heart volume and the blood volume of heart and lungs. This is quite natural as there is reason to expect that a dilatation of the heart should be followed by a considerably increased quantity of residual blood in the heart.

Considering case 1, which afterwards went to autopsy, the quantity of residual blood of the heart during life was determined with the guidance of the ante- and postmortem roentgenologic determination of the heart volume and by the postmortem quantity of residual

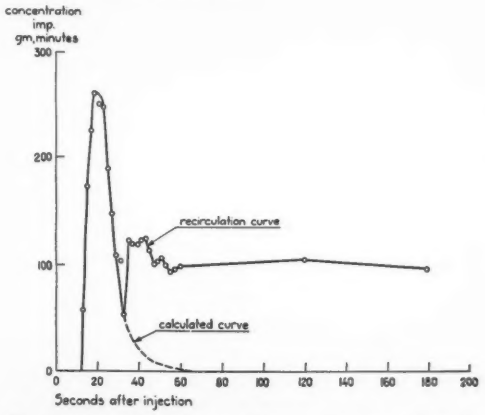

FIG. 5.—DILUTION CURVE, NORMAL SUBJECT (Case 5).

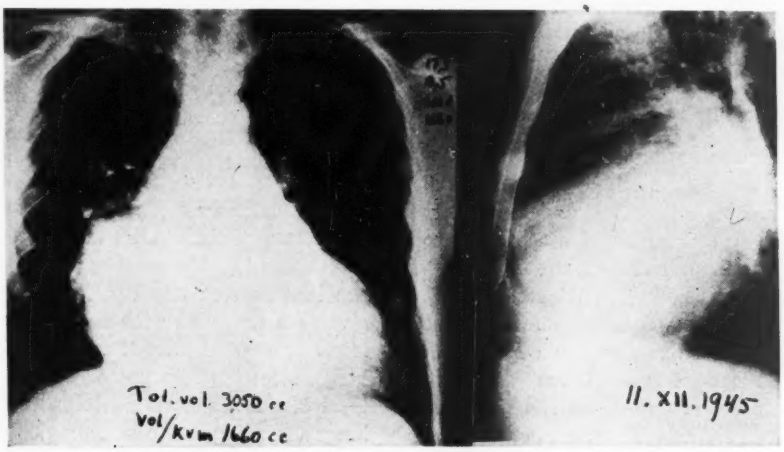

FIG. 6.—X-RAY OF THE HEART, CASE 1. Heart volume = 3.1 liters.

blood. As a control, the displacement volume of the extracted heart was determined.

The following results were obtained: roentgenologic heart volume in vivo, 3.1 liters; roentgenologic heart volume after death, 2.2 liters; residual blood of the heart: 1.1 liters; displacement volume of the extracted heart, 2.2 liters.

It is evident from these results (1) that the roentgen volume diminished 0.9 liter at the moment of death, and 0.9 liter of blood must accordingly then have been pressed out of the heart, as it cannot be imagined that the heart muscle should have undergone such a considerable reduction; (2) that the blood volume of the heart in vivo had been 2.0 liters, and as the stroke volume is of the size 0.1 liter there is evidently here a very large quantity of residual blood.

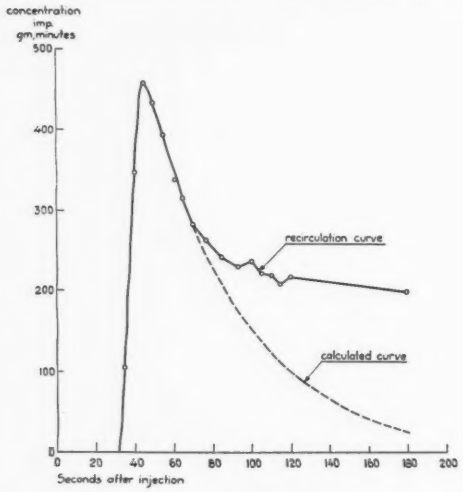

FIG. 7.—DILUTION CURVE, CASE 1.

The values of cardiac output, obtained by this method are as a rule higher than those obtained with the Fick method, as an arterial puncture cannot be executed under as quiet circumstances as a determination according to the gas-analytical method. As to the determination of the pool volume, this increase is at least partly compensated by a decrease of the time Δt and an increase of the constant λ. The injection has generally taken place five to fifteen minutes after the arterial puncture to create at least as quiet circumstances as possible. The results of the original measurments for two of the cases are to be found in tables 3 and 4. Corresponding curves and x-ray of the heart are found in figures 4–7.

ERROR OF CALCULATION

From equation 10 we get through logging and differentiation:

$$\frac{dX_1}{X_1} = \frac{dv_i}{v_i} + \frac{dc_i}{c_i} - \frac{dn_1}{n_1} + \frac{dh_i}{h_i} - \frac{dh}{h}$$

where n_1 = the denominator = $R + \int_H^\infty c' \cdot e^{-\lambda t}\, dt$

$$\frac{dv_i}{v_i} = 2 \text{ per cent} \qquad \frac{dc_i}{c_i} < 2 \text{ per cent}$$

$$\frac{dh_1}{h_1} = \frac{dh}{h} < 1 \text{ per cent}$$

$\frac{dn_1}{n_1}$, depending both on R and the integral. R can be determined with fairly good accuracy. However, concerning the integral, even small variations in λ may cause rather great variations of the integral value. The uncertainty of the integral value amounts to some 10 per cent.

For the above stated cases

in the normal case: $\frac{dn}{n} = 5$ per cent

in Case 1: $\frac{dn}{n} = 6$ per cent

$\frac{dX_1}{X_1} = 10$ per cent. That is, the uncertainty in determining the cardiac output amounts to about 10 per cent.

SUMMARY

An indicator substance, P^{32}, has been injected into an arm vein. Immediately afterward blood samples have been taken at about three-second intervals from the artery of the opposite arm. The concentration of indicator of the obtained samples has been drawn up as a function of time. A formula has been given for estimating the cardiac output from the obtained curve. Moreover, formulas have been given for estimating the upper as well as the lower limit of the blood volume in heart and lungs. It seems that 29 to 35 per cent of the total blood volume is contained in heart and lungs according to the measurements obtained.

Appendix: Symbols

A Point in fig. 1
A_1 Point in fig. 3
a The largest diameter in Equation 13
a_1 and a_4 The largest diameters perpendicular to a_2 and to each other
B Point in fig. 1
B_1 Point in fig. 3
c Indicator concentration at testing point (variable)
c' Constant in Equation 2
C_1 Point in fig. 3
c_1' Concentration at Point C_1
c_p Mean pool concentration at the time N (fig. 1); derived from primarily circulating indicator
c_h Concentration in samples taken twenty to sixty minutes after injection
c_i Concentration of injected material
c_m Mean concentration in the receptacles
c_2 Concentration at Point P_2
c_3 Concentration at Point P_3
D Point in fig. 1
D_1 Point in fig. 3
E Length in fig. 1
e Base of the natural log. system (appr. 2.72)
F Length in fig. 1
f_1 A function
f_2 A function
G Point in fig. 1
H Point in fig. 1
h Hematocrit in the body
h_i Hematocrit in the injected material
J Point in fig. 1
K Point in fig. 1
K_1 Total blood volume in the body (used in table 1)
K_2 Constant in Equation 13
L Point in fig. 1
m Amount of indicator in the receptacles
m_0 Integration constant
m_1 Amount of primarily circulating indicator in heart and lungs at the time interval H-N (fig. 1)
N Point in fig. 1
n $R + \int_H^\infty c' e^{-\lambda t}\, dt$
P_2 Point in fig. 1
P_3 Point in fig. 1
R Area between segment $DAGH$ and t-axis
S A factor $(>1) = \frac{c_1'}{c_m}$
S_1 A factor $(>1) = \frac{c_2}{c_p}$
t General time nomenclature
t_2 Time in fig. 1
t_3 Time in fig. 1
Δt Time interval in fig. 1
V Volume of the receptacles
V_p Pool volume
V_t Total blood volume in the body
V_0 Mean value of V_1 and V_2
V_1 Upper limit of pool volume
V_2 Lower limit of pool volume
v_i Volume of injected blood
X Rate of flow in receptacles
X_1 Cardiac output
α Constant in Equation 1
λ Slope of the line in Equation 1

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The Electric Field of an Eccentric Dipole in a Homogeneous Spherical Conducting Medium

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The electrical position of the heart with reference to the electrodes used in studying its field is unknown. For reasons presented, it is more likely eccentric; hence, the equation defining the field of an eccentric dipole in a spherical medium might be useful for projected experimental studies and for better understanding of the way in which a given electrical position determines the electrode potentials. A method introduced by Helmholtz was used for deriving the desired equation. It is discussed since its concepts are of considerable importance to other electrocardiographic problems, too. The more simple mathematical example dealing with the centric dipole in the sphere is discussed. The equation for the field of the eccentric dipole is given and data based upon it are presented in numerical and map form. The Helmholtz equation for the field in the spherical conductor produced by two small spherical electrodes arbitrarily located is also presented and briefly discussed.

TWO of the assumptions upon which the equilateral triangle of Einthoven is based are: (1) that the electric field generated by the heart may be regarded as not significantly different from that of a current dipole at the center of a homogeneous spherical conductor, and (2) that this origin is equidistant from the apices of the triangle defined by the standard limb leads. It is, of course, obvious that these assumptions disregard the eccentric location of the human heart, which is, at least in the geometric sense, considerably nearer the left than the right shoulder, and much farther from the junction of the left leg with the trunk than from the right shoulder. It is also much closer to the anterior than to the posterior surface of the chest. The spatial relations suggest, therefore, that its field may resemble that of an eccentric dipole more closely than that of a centric dipole. For this reason it seemed to us that the equation which defines the field of an eccentric dipole in a spherical medium might prove useful in connection with a projected experimental study of the field established by connecting electrodes placed on the precordium of the living subject, or in the heart of a cadaver, to a current source.

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So far as we know, this particular equation is not available in the literature, but equations which define fields similar to that under consideration are well known, and Helmholtz[1] long ago developed a method by which all problems relating to the distribution of steady currents in a spherical conductor can be solved.

Helmholtz also gave the expression for the potential at any point in such a medium when the input electrodes are on its surface. We have employed this method to obtain the equation sought and this will be better understood if some account of the manner in which it was derived is given. We take this occasion, therefore, to call attention to the importance of the article cited for those who are concerned with bioelectric phenomena, and to mention some matters discussed therein which have a bearing on electrocardiographic problems not directly related to our present subject.

Important Principles Bearing on the Distribution of Bioelectric Currents

Five years hence, a century will have passed since Helmholtz, a young man, 32 years of age, who had already made important contributions to theoretic physics, had been the first to measure the speed of the nerve impulse, and who had invented the ophthalmoscope, became interested in the bioelectric investigations of his friend, Emil du Bois Reymond. The result of this interest was an article, published in 1853, on the distribution of electric currents in volume conductors, which came very close to

exhausting the subject. It seems strange that there are so few references to this article in the literature concerned with the electrocardiogram and related subjects. It is listed in the bibliography of the book by Kraus and Nicolai[2] published in 1910, but there is, so far as we know, no mention of it in the writings of Waller, Einthoven, or Lewis.

We do not propose to review the contents of this article in detail, but merely to present without proof its more important theorems and to explain how we have made use of them for the purpose stated in the preceding paragraph. The fundamental principles stated and explained by Helmholtz may be considered under three headings:

1. *The Principle of Reciprocity.* We shall not try to state this theorem in the exact form which Helmholtz gave it, but only to give some idea of its scope and significance. Let there be given a volume conductor of arbitrary shape and either homogeneous or heterogeneous with respect to its electrical properties, and two pairs of electrodes arbitrarily located within it. If electrodes A and B of one pair are employed to pass a current i through the volume conductor, the resulting potential difference between C and D, the electrodes of the other pair, must be the same as the potential difference between A and B when a current of magnitude i enters the conductor by way of C and D. In other words, the result of this hypothetic experiment is not altered by interchanging the connections to the detector and the connections to the generator. A few experiments performed recently indicate that this principle holds when the volume conductor is the body of a living subject and the current is one alternating twenty-five times per second. We may conclude, then, that when a current of a given magnitude i flows out of the heart through one of the elements, a, of its surface and returns to the heart through another element, b, the resulting potential difference between two electrodes, one on each arm, is equal to the potential difference between a and b when a current i enters the body by way of the arm electrodes.

2. *The Principle of Superposition.* Let there be given a system of conductors within which electromotive forces are arbitrarily distributed. The currents and the potential differences due to all these electromotive forces acting together are the same as those obtained by adding algebraically all the currents and potential differences that would be produced by the individual electromotive forces, each acting independently. And furthermore, the components, parallel to three mutually perpendicular axes, of the current flowing at a given point when all the electromotive forces are acting simultaneously, are each equal to the algebraic sum of the corresponding components when each of the electromotive forces is acting independently.

Such experimental evidence as is pertinent indicates that this principle is applicable to the electromotive forces generated by the heart. It is known, for example, that when the auricles and ventricles are activated simultaneously the auricular and ventricular deflections are summed algebraically, and that algebraic addition of the dextrocardiogram and the levocardiogram produces a replica of the bicardiogram.

3. *The Principle of the "Electromotive Surface."* This might also be called the principle of the Helmholtz double layer. The "electromotive surface" or double layer is, in fact, a layer of dipoles so placed that their axes are perpendicular to the surface on which they lie. Across such a layer of dipoles there is a potential difference of $4\pi M$ where M is the electric moment per unit area of surface.

The theorem states that for every conductor A in the interior of which there are arbitrary electromotive forces there is a double layer, which, if located on the surface of A, will produce in a second conductor, B, when this is brought into contact with A, the same currents and potential differences as would be produced there by the internal electromotive forces of A acting alone under the same circumstances. The proof of this theorem depends upon the principle of superposition. The principle of the "electromotive surface," in the form in which it is applicable to networks was rediscovered by Thévenin[3] some thirty years after it was first stated by Helmholtz, and in most texts on electrical engineering it is called "Thévenin's theorem."

The hypothetic method of finding the double-layer specified by the theorem in a given case is described by Helmholtz somewhat as follows: Assume that conductor A with its internal electromotive forces is isolated from all others. Choose any element of its surface and measure the difference in potential between it and each of the other surface elements. On each of these other elements place a double layer so constituted that the potential of its outer surface with respect to that of its inner surface is the same as the potential of that element with respect to the potential of the reference element. The double layer obtained by this imaginary procedure is the one sought and we shall call it the specified double layer, and designate its potential function by the symbol P. Now the sign of the potential function of a double layer can be reversed at every point by reversing the positions of the positive and negative poles of its component dipoles. The potential function of the double layer which is the inverse (of that) of the specified double layer may then be represented by the symbol, $-P$. We shall call this double layer the inverse double layer. When it is substituted for the specified double layer all parts of the surface of conductor A will be at the same potential and no current will flow in the second conductor B, containing no electromotive forces of its own, when it is brought into contact with A to form the system AB. According to the principle of superposition we may say, then, that at all points of the conductor B the potential function $(-P)$ of the inverse double layer is equal in absolute magnitude and opposite in sign to the potential function (W_1) of the interior electromotive forces of A. We have then the equation,

$$W_1 - P = 0, \text{ or } W_1 = P, \qquad (1)$$

which states that when the internal electromotive forces of A and the inverse double layer are acting together in the combined conductor AB there is no field in B, and that the specified double layer acting alone upon AB would produce in B currents and potential differences identical with those that would be produced by the internal forces of A acting alone upon the same system.

Consider now conductor A before, and again after, it has been brought into contact with B to form the system AB. Let W_0 be the potential function of the internal forces of A at any point of A before this conductor is brought into contact with B, and W_1, the potential function of these internal forces at the same point after A has been brought into contact with B. The inverse double layer prevented any flow of current in B when it was brought into contact with A, and consequently, the effect of this double layer and the internal forces of A acting together upon the system AB produced in A the same field as the interior forces of A acting alone upon A before it was brought into contact with B. Hence, we have the equation,

$$W_0 = W_1 - P, \text{ or } W_1 = W_0 + P, \qquad (2)$$

which states that the currents and potential differences in A after it has been brought into contact with B to form the system AB are the algebraic sums of the currents and potential differences produced in A, before it was brought into contact with B, by its internal forces alone, and the currents and potential differences produced in A, after it was brought into contact with B, by the specified double layer acting alone.

It is clear that the only part of the double layer, specified or inverse, that is essential to the argument is that which lies on that part of the surface of A subsequently brought into contact with B. Helmholtz pointed out that when the latter is a network of linear conductors which is brought into contact with A at only two points, P_1 and P_2, the volume conductor, so far as any observations on B are concerned, may be replaced by a resistance R and a voltage E. The resistance R of A is measured between P_1 and P_2, and E is the potential difference between these two points before A is brought into contact with B. If the electromotive forces of A are constant the inverse double layer in this case is equivalent to a battery with a voltage equal to the open-circuit potential difference between P_1 and P_2 and connected in such a way as to oppose this potential difference. The specified double layer is simulated by reversing (the contacts) of this battery.

In their recent book, Gardner and Barnes[1]

write in reference to this principle in the form in which it was stated by Thévenin: "When written, this theorem pertained to the direct-current, steady-state behaviour of networks, but it has been generalized since to alternating currents and transients."

This principle has a very important bearing upon many of the questions which arise in studies concerned with the electrical field of the heart. It makes it possible to predict what kind of changes in this field would result if a part of the heart's surface were short-circuited or insulated from the neighboring tissues, or if part or all of the body were immersed in a conducting field. It shows that the voltages acting in the standard limb leads, taken one at a time, are always the open-circuit potential differences between the limb electrodes, even when these leads are taken with a low-resistance instrument, such as a string galvanometer. It is the principle upon which is founded Einthoven's law that the algebraic sum of the deflections in Leads I and III is equal to the deflection in Lead II. Helmholtz discovered the principle and confirmed it experimentally before Einthoven was born by showing that such a law held for a field generated in a lump of carbon, but it is quite certain that Einthoven was never aware of this earlier work. Neither the principle nor the law is valid when the circumstances are such that bringing the conductor B into contact with A results in a flow of current through a polarizable element and consequently in a counter electromotive force. Helmholtz made this observation in one of his experiments in which the volume conductor was a solution of copper sulfate in a glass vessel.

The Equation for the Field of an Eccentric Dipole

We shall now consider the method described by Helmholtz for finding the potential function of a known electromotive force in a spherical homogeneous volume conductor, and its application to the problem of obtaining an expression which defines the field of an eccentric dipole in such a medium. This method is founded on the known equations for the potential at any point outside or inside a spherical surface bearing a layer of positive charges varying in number per unit area from point to point. The equations are:

$$V_0 = \frac{1}{r} F(\theta, \phi, U), \qquad U = \frac{R}{r} \tag{3}$$

and

$$V_i = \frac{1}{R} F(\theta, \phi, V), \qquad V = \frac{r}{R}. \tag{4}$$

The first of these equations gives the potential at any outside point, and the second the potential at any inside point, when R is the radius of the spherical surface, r is the distance of the outside point or inside point, as the case may be, from the center of this surface, F is almost any continuous function, and θ and ϕ are the angles which define the direction from the origin of the point at which the potential is to be evaluated.

Helmholtz showed that by differentiating Equations (3) and (4) with respect to R, it is possible to obtain the corresponding equations applicable when the single layer of positive charges is replaced by a layer of negative charges on a spherical surface of radius $R - \Delta R$ and a layer of positive charges on a spherical surface of radius $R + \Delta R$. It is to be understood that the new positive charges are each equal in number and magnitude to the original charges, that the two new spherical surfaces are concentric with the original surface, and that ΔR is an infinitesimal. The double layer thus obtained is equivalent to a layer of dipoles. We then have the expressions:

$$P_0 = 2 \frac{dV_0}{dR} \Delta R = \frac{2}{r^2} F'(U) \Delta R, \tag{5}$$

and

$$P_i = 2 \frac{dV_i}{dR} \Delta R = -\frac{2}{R^2} \left[F(V) + \frac{r}{R} F'(V) \right] \Delta R, \tag{6}$$

in which

$$F'(U) = \frac{dF(U)}{dU},$$

and

$$F'(V) = \frac{dF(V)}{dV}.$$

Assume that the potential function (W) of a given electromotive force is known when the conductor in which it exists is infinite and homogeneous. The problem is to find the double layer, that, located on a spherical surface of given radius surrounding the site of the known electromotive force, will have the same potential function as this force at points outside the surface on which it lies. It is clear that if such a double layer can be found, the inverse double layer will cancel that part of the field of the given electromotive force which extends beyond the spherical surface. The currents and potential differences inside this surface will then be the algebraic sums of those determined by the potential function of the electromotive force and those determined by that of the inverse double layer. For points outside the spherical surface we have then the equation:

$$W - P_0 = 0; \qquad W = P_0 = \frac{2}{r^2} F'(U)\Delta R; \qquad F'(U) = \frac{r^2}{2\Delta R} W. \tag{7}$$

Consequently,

$$F(U) = \frac{1}{2\Delta R} \int r^2 W \, dU + c, \tag{8}$$

where c is an arbitrary constant. Having found $F(U)$ we can find $F(V)$ and finally S, the potential inside the spherical surface, from the equations,

$$S = W - P_i, \tag{9}$$

and

$$S = 2\left[\frac{1}{R^2} F(V) + \frac{1}{r^2} F'(U) + \frac{r}{R^3} F'(V)\right]\Delta R, \tag{10}$$

As an illustration of the procedure involved, we may consider the simple case of a centric dipole in a sphere of radius R. The potential function of a dipole in an infinite medium is given by the expression,

$$V_P = M \frac{\cos\theta}{r^2}, \tag{11}$$

where M is the moment of the dipole, r is the distance of the point p where the potential V_P is measured, and θ the angle between the positive direction of the axis of the dipole and the radius vector to that point. We have

$$W = P_0 = \frac{M}{r^2}\cos\theta, \qquad F'(U) = \frac{M}{2\Delta R}\cos\theta,$$

$$F(U) = \frac{MU\cos\theta}{2\Delta R}, \qquad F'(V) = \frac{M}{2\Delta R}\cos\theta, \tag{12}$$

$$\text{and} \qquad F(V) = \frac{Mr\cos\theta}{2R\Delta R}.$$

$$S = 2M\cos\theta\left[\frac{r}{2R^3\Delta R} + \frac{1}{2r^2\Delta R} + \frac{r}{2R^3\Delta R}\right]\Delta R \tag{13}$$

or

$$S = M\cos\theta\left[\frac{1}{r^2} + \frac{2r}{R^3}\right],$$

which is correct.

In order to find the equation for the field of an eccentric dipole in a spherical medium the potential function of the dipole for an unrestricted medium must be expressed in a form different from that employed in the case of the centric dipole. As the origin of our coordinate system we choose the center of the spherical surface with reference to which the dipole is eccentric and is to become the boundary of the conducting medium. Let R be the radius of this surface, fR the distance of the dipole from the origin, λ_1, μ_1, ν_1 the direction cosines, with respect to the coordinate axes, of the radius vector to the dipole, r, the distance of the point p from the origin, λ, μ, ν the direction cosines of the radius vector to this point, and γ the cosine of the angle between the radius vector to the dipole and the radius vector to p. For γ we have

$$\gamma = \lambda\lambda_1 + \mu\mu_1 + \nu\nu_1. \tag{14}$$

The distance of the point p from the dipole is given by the expression,

$$[r^2 + (fR)^2 - 2rfR\gamma]^{1/2}, \tag{15}$$

and the direction cosines of the line from the dipole to p are

$$\frac{r\lambda - fR\lambda_1}{[r^2 + (fR)^2 - 2rfR\gamma]^{1/2}}, \quad \frac{r\mu - fR\mu_1}{[r^2 + (fR)^2 - 2rfR\gamma]^{1/2}}, \quad \frac{r\nu - fR\nu_1}{[r^2 + (fR)^2 - 2rfR\gamma]^{1/2}}. \tag{16}$$

If the direction cosines of the axis of the dipole are ψ_x, ψ_y, ψ_z the cosine of the angle

between this axis and the line from the dipole to p is the sum of the products formed by multiplying each of these direction cosines by the corresponding direction cosine of the three given in Equation (16). The resulting expression multiplied by the moment M of the dipole and divided by the square of the distance (Equation 15) of the point p from the dipole gives for the potential, V_P, at p when the medium is unrestricted, the expression

$$V_P = M\frac{\psi_x(r\lambda - fR\lambda_1) + \psi_y(r_\mu - fR\mu_1) + \psi_z(r\nu - fR\nu_1)}{[r^2 + (fR)^2 - 2rfR\gamma]^{3/2}}. \tag{17}$$

We shall not take up the space that would be needed for the details of the remainder of the calculations required to transform this equation into that for the spherical medium, since the principle and the method involved have already been fully explained. The final equation is

$$V_P = M\psi_x\left\{\frac{r\lambda - fR\lambda_1}{(r^2 + f^2R^2 - 2rfR\gamma)^{3/2}} + \frac{rR\lambda - r^2f\lambda_1}{R(R^2 + r^2f^2 - 2rfR\gamma)^{3/2}} + \frac{(rf - R\gamma)\lambda - (rf\gamma - R)\lambda_1}{fR^2(1-\gamma^2)(R^2 + r^2f^2 - 2rfR\gamma)^{1/2}} + \frac{\gamma\lambda - \lambda_1}{fR^2(1-\gamma^2)}\right\} \tag{18}$$

plus four terms of similar form in which ψ_y, μ, and μ_1 replace ψ_x, λ, and λ_1 and four more in which ψ_z, ν, and ν_1 replace ψ_x, λ, and λ_1.

When the point p at which the potential is to be evaluated is on the surface of the spherical conductor, r is equal to R and this equation reduces to a considerably less complicated one, i.e.,

$$V_p = \frac{M\psi_x}{R^2}\left\{\frac{2(\lambda - f\lambda_1)}{(1 + f^2 - 2f\gamma)^{3/2}} + \frac{(f-\gamma)\lambda - (f\gamma - 1)\lambda_1}{f(1-\gamma^2)(1 + f^2 - 2f\gamma)^{1/2}} + \frac{\gamma\lambda - \lambda_1}{f(1-\gamma^2)}\right\} \tag{19}$$

plus six additional terms corresponding to the eight additional terms in Equation (18).

The equation corresponding to Equation (18) which defines the field in a homogeneous spherical conductor when a current J enters it by way of a small spherical electrode, S, and leaves it by an identical electrode, S', is

$$V_p = \frac{J}{4\pi\sigma}\left\{\frac{1}{R}\log e\left[\frac{1 - f_2f_3\gamma_2 + (1 + f_2^2f_3^2 - 2f_2f_3\gamma_2)^{1/2}}{1 - f_1f_3\gamma_1 + (1 + f_1^2f_3^2 - 2f_1f_3\gamma_1)^{1/2}}\right] + \frac{1}{R(f_3^2 + f_1^2 - 2f_1f_3\gamma_1)^{1/2}} - \frac{1}{R(f_3^2 + f_2^2 - 2f_3f_2\gamma_2)^{1/2}} + \frac{1}{R(1 + f_1^2f_3^2 - 2f_1f_3\gamma_1)^{1/2}} - \frac{1}{R(1 + f_2^2f_3^2 - 2f_2f_3\gamma_2)^{1/2}}\right\}. \tag{20}$$

In this expression, R is the radius of the spherical conductor, σ its specific conductivity, f_1R and f_2R the distances of the input electrodes S and S' from the center of the conductor, f_3R the distance of the point p from the center of the conductor, γ_1, the cosine of the angle between the radius vector to S and the radius vector to p, and γ_2 the cosine of the angle between the radius vector to S' and the radius vector to p. When f_1 and f_2 are each equal to 1, this equation reduces to that given by Helmholtz.

The last term in the second member of Equation (18), and the same term in Equation (19), represent the value of the integral in Equation (8) when U is equal to zero. No corresponding term occurs in the equation for the centric dipole, Equation (20), or the equation given by Helmholtz, for in these cases the integral vanishes when U becomes zero. In the case of the eccentric dipole this integral must be regarded as a definite integral with the upper limit U and the lower limit zero.

It will be observed that Equation (18) does not, as might be expected, reduce to the equation for the centric dipole when f is replaced by zero; for, when this is done, the last two terms of the second member appear to become infinite (note that λ_1 and γ are not defined when the dipole is centric) and their sum takes the indeterminate form zero divided by zero. By the proper methods of finding the limiting value of such indeterminate expressions, it can, however, be shown that as f approaches zero the sum of the twelve terms of the second member of Equation (18) approaches as a limit the second member of Equation (13).

The expressions which give the potential at the ends of that diameter of the spherical medium which passes through the eccentric dipole are of simple form. For the end of this diameter which is nearer the dipole, the po-

tential is given by the expression,

$$V_p = \frac{M \cos\theta}{R^2} \frac{3 - f}{(1 - f)^2} \tag{21}$$

For the opposite end of this diameter, the corresponding expression is

$$V_p = \frac{M \cos\theta}{R^2} \frac{3 + f}{(1 + f)^2} \tag{22}$$

In these last two equations, θ is the angle between the axis of the dipole and the diameter specified.

obtaining information as to the possible effects of the heart's eccentric position upon the deflections in the standard or unipolar limb leads. It is, however, more particularly helpful in connection with the analysis of the results obtained in experiments in which an electric field is set up in the body by connecting two electrodes in contact with it to a current source. In the discussion of electric fields that are to be compared with that of the heart it is desirable, because of the conventions that have been

TABLE 1.—*Potential values (V_R, V_L, V_F) at the limb electrodes and their differences (LI, LII, LIII) calculated with equation (19) for giving arbitrarily chosen eccentric positions (a, b, c, d, e) of the dipole for a comparison with those due to the centric position (f). In each dipole position the potentials are determined for both the horizontal (H) and the vertical (V) directions of the dipole axis. (See figure 1 for a map of these data in Burger triangles).*

	Eccentric Dipole				Position of Axis	V_R	V_L	V_F	I	II	III
	f	λ_1	μ_1	ν_1							
(a)	0.5	0	−1	0	H	−3.82	3.82	0	7.64	3.82	−3.82
					V	−0.31	−0.31	1.55	0	1.86	1.86
(b)	0.25	1	0	0	H	−1.95	3.51	−0.58	5.46	1.37	−4.09
					V	−0.92	−2.72	2.80	−1.80	3.72	5.52
(c)	0.25	0.866	−0.5	0	H	−2.24	4.23	−0.37	6.47	1.87	−4.60
					V	−0.86	−2.44	2.37	−1.58	3.23	4.81
(d)	0.25	0	1	0	H	−1.87	1.87	0	3.74	1.87	−1.87
					V	−1.51	−1.51	4.89	0	6.40	6.40
(e)	1	0	0	1	H	−1.22	1.22	0	2.44	1.22	−1.22
					V	−0.71	−0.71	1.41	0	2.12	2.12
(f)	0	Centric Dipole			H	−2.60	2.60	0	5.20	2.60	−2.60
					V	−1.50	−1.50	3.00	0	4.50	4.50

An estimate of the error in surface potentials made by considering two small input electrodes equivalent to a doublet is given by

$$V_p = \frac{3M \cos\theta}{R^2} \left(1 - \frac{7a^2}{6R^2}\right) \tag{23}$$

in which a is one half the distance between the centers of the electrodes. This equation is applicable to the case in which the input electrodes are equidistant from the center of a homogeneous spherical medium of radius R. The corresponding equation for the case in which the input electrodes are equidistant from an eccentric point is too complicated to be useful. The equation given is based on a similar one developed by Dr. Kenneth S. Cole.

Illustration Examples

Equation (19) may be used for the purpose of

adopted in electrocardiography, to choose as coordinate axes the following lines:

Horizontal or X-axis: A line extending from the origin toward the left limit of the cardiac field.

Vertical or Y-axis: A line extending from the origin toward the inferior or caudal limit of the cardiac field.

Sagittal or Z-axis: A line extending from the origin toward the posterior or dorsal limit of the cardiac field.

The results of some calculations based on Equation (19) are given in table 1. This table gives the value of f, λ_1, μ_1, and ν_1 assumed in each of five examples. The potentials calculated were those of the apices R, L, F of an equilateral triangle lying in the great circle of a spherical conductor of unit radius, in the XY plane, and in the same position as the

Einthoven triangle. The symbols V_R, V_L, and V_F, I, II, and III have the significance attached to them in discussions of the electrocardiogram. The potentials of the apices of the triangle and the differences in potential between them were computed for two positions of the dipole axis: the horizontal position, H, in which the axis is parallel to the X-axis; and the vertical position, V, in which it is parallel to the Y-axis. The moment of the dipole is taken as unity. The direction cosines given are with respect to the axes specified. In Example (a) the eccentric dipole is at the center of that side of the equilateral triangle which corresponds to Lead I. In Example (b) it is on the positive X-axis; in (c) it is on the line from the origin to the L apex; in (d) it is on the Y-axis below the origin; in (e) it is on the Z-axis at the posterior surface of the spherical conductor. For comparison, the data for a centric dipole (f) of unit moment are added at the end of the table.

In figure 1 the data contained in table 1 are presented in graphic form. The triangles shown there were constructed by the method devised by Burger and van Milaan[5] which is based on the concept that the deflection in a given lead may be regarded as the scalar product of two vectors. One of these vectors represents the lead, and the other represents the electromotive force responsible for the field. In the cases under consideration, it is assumed that the moment of the dipole is equal to 1 and the second vector is, therefore, of unit length. Under the circumstances the lead vector is the hypotenuse of a right triangle. The altitude of this triangle is equal to the deflection in the given lead when the axis of the dipole is vertical, and the "base" is equal to this deflection when the axis of the dipole is horizontal. When data of the kind listed in table 1 are available, the simplest method of constructing the Burger triangle is to select some point as origin and locate its apices. To locate the F apex of the triangle (*a*), for example, it is necessary only to find on the positive Y-axis a point distant 1.55 units from the origin. To find the L apex required the location of a point distant 3.82 units from the positive X-axis and 0.31 units from the negative Y-axis.

The Burger triangle may be regarded as a kind of map which gives all the information concerning an electric field obtainable by meas-

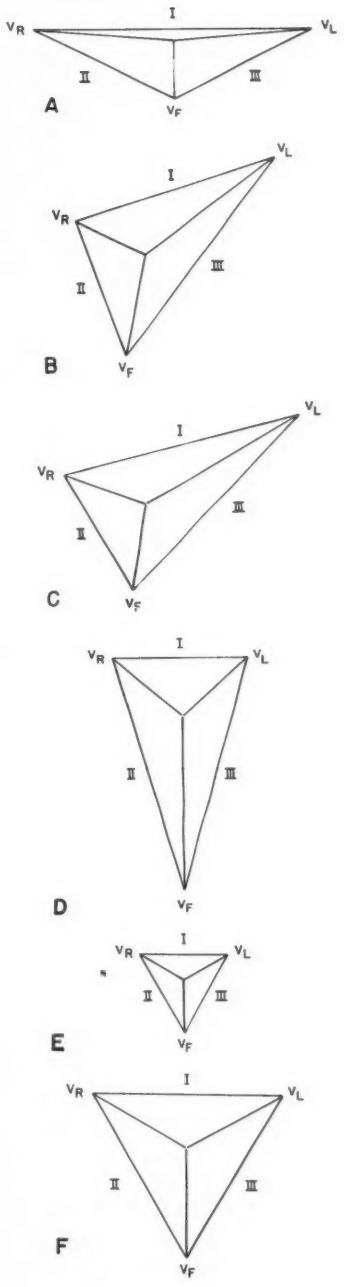

FIG. 1.—Data in table 1 presented in graphic form.

uring the potential differences between the three electrodes. In the hypothetic cases under consideration the true potentials of the electrodes are given for the two positions of the electrical axis. Consequently, the origin, 0, in the triangles of figure 1 represents a point in the field which is at zero potential. The lengths of the lines from this point to the apices of the triangle and from one apex to another are equal to the difference in potential between the two ends of that line when the axis of the dipole is parallel to it.

When the volume conductor is homogeneous and spherical, the dipole is centric, and the electrodes are on the surface of the conductor, the Burger triangle has exactly the same shape as the geometric triangle defined by the three lead electrodes. Under other circumstances, the shape of the former varies not only with the locations of the lead electrodes, but also with the shape, size, and nature of the volume conductor, and the site of its internal electromotive force.

Figure 1 and table 1 show that changes in the shape of the equilateral Burger triangle which depicts the field of a centric dipole in a spherical medium (f) produced by shifting the dipole to an eccentric position are in essence quite simple. When the dipole is moved toward the center of a given side of the triangle (*a*) that side becomes longer than the other two; when it is moved toward a given apex, Examples (c) and (d), the two sides of the triangle meeting at that apex become longer than the third side; when it is moved in a direction perpendicular to and away from the plane defined by the lead electrodes, Example (e), all of the sides of the triangle shorten to the same extent. Other displacements of the dipole may be considered combinations of these three. Triangles (*a*), (*c*), and (*d*) of figure 1 are isosceles. In (*a*) the horizontal side is longer; in (*d*) it is much shorter than the other two sides. In (*c*) the side corresponding to Lead II is shorter than those which correspond to Leads I and III. It may be pointed out that Burger triangles identical with these in shape could be obtained by shifting the lead electrodes instead of the dipole. If this were done, it would, however, be necessary in case (*a*) to locate these electrodes in such a way as to place the centric dipole outside the geometric triangle formed by the three leads.

Summary

Attention is called to the importance of the contribution made by Helmholtz to our knowledge of the distribution of electric currents, particularly bioelectric currents in volume conductors.

The equation which defines the potential function of an eccentric dipole in a homogeneous spherical medium is presented and discussed.

It is hoped that the equation will prove useful in connection with the analysis of the results of experiments in which an artificial electric field is established in the trunk by connecting electrodes placed on the precordium of a living subject, or in the heart of a cadaver, with a current source.

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Atrophy of the Heart: A Correlative Study of Eighty-Five Proved Cases

By H. K. Hellerstein, M.D., and D. Santiago-Stevenson, M.D.

This critical study of atrophy of the heart is based upon a detailed analysis of 85 proved cases. The clinical, roentgenographic and electrocardiographic features are considered to be sufficiently distinctive to facilitate antemortem recognition. The clinical implications of atrophy of the heart and the reversibility of atrophy and hypertrophy are emphasized.

ATROPHY of the heart is defined as an acquired reduction in the size and mass of this organ. While hypertrophy has been the subject of considerable study and investigation, the entity of atrophy has been in the main overlooked and neglected. Rarely do modern textbooks on cardiology mention it, and then only to dismiss it with a few lines pointing to its rarity and lack of clinical significance. However, recent reports on the effects of prolonged bed rest[23–34] and starvation[35–44] on the cardiovascular system have focused attention on the reversible changes occurring in the hearts of such patients which appear to be comparable to those occurring in cardiac atrophy. For this reason it was thought advisable to study atrophy of the heart, placing particular emphasis on the following aspects: (1) incidence, (2) etiologic factors, (3) gross and microscopic pathologic features, (4) clinical, radiologic and electrocardiographic picture, and (5) cardiovascular functional status.

Material and Methods

The protocols of 2,000 consecutive autopsies performed in the Institute of Pathology, Western Reserve University, between March 31, 1941, and October 21, 1946, were reviewed. The 85 cases in which the diagnosis of atrophy of the heart had been made were selected for further study and analysis. The clinical histories, electrocardiographic tracings, x-ray films of the chest and pathologic sections of the heart were re-examined and analyzed in detail. These observations, and their correlation, together with a survey of the literature available on the subject, form the material for this report.

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Historical Review

Atrophy of the heart has been recognized since the birth of morbid anatomy. According to Gibson,[1] atrophy of the heart was described for the first time as a definite pathologic entity by Riolan in 1649.[2] The first full description, however, including clinical observations, was recorded by Senac in his Treatise on Heart Disease (1749).[3] Senac recognized that hearts with diminished volume were the result of chronic systemic diseases, and cited an instance from his personal experience of a soldier who was found to have a very small heart covered by thickened pericardium. He claimed that the ancients were aware of "phthisie" of the heart and that even the Kings of Egypt recognized this condition among cadavers. He considered palpitation as the only symptom of atrophic hearts and mentioned the juice of horse-radish as the only efficacious remedy.

Burns[4] (1809) in his book on diseases of the heart devoted a section to atrophy. Bertin[5] (1833) classified atrophy into the following morphologic groups: (1) Concentric type—the cavity is diminished in size, but the wall remains the same. (2) Aneurysmal type—the walls are markedly thinned and the heart chambers dilated. (3) Simple type—the muscular walls are thinned with little change in the volume of the heart. Bouillaud[6] (1841) followed this same classification and gave a detailed clinical description which has since been unexcelled. He pointed out the fallacy of using the thickness of the ventricular wall, particularly in the concentric type, as an index of atrophy. In such cases the wall may appear normal or relatively more thickened than normal while the heart weight may be one-third or one-fourth of the normal. He presented 7 cases of atrophy with

an average heart weight of 175 grams, and emphasized that the weight and volume do not diminish in the same degree. Clinically, the following features were noted: distant heart sounds, diminished precordial activity, decreased precordial dullness, and small and narrow pulse. Atrophy was considered to be secondary to local factors, such as prolonged compression by pericardial effusion, or to generalized illnesses during which there is inadequate nutrition, such as the marasmus secondary to chronic disease of the gastrointestinal organs, tuberculosis, cancers, and typhoid fever.

Stokes[7] (1855) met this condition particularly in patients dying of chronic tuberculosis and considered the process as part of the general absorption of all muscular tissues resulting in diminution of volume and power. Bamberger[8] in his Lehrbuch der Krankenheiten des Herzen (1857) gave a first-hand description of the appearance of such hearts at autopsy. He stated that atrophy appears diffusely throughout the organ and may be so great as to produce reduction in size to one-half of the original volume and weight. The heart appears pale with diminution, in most cases, of the surrounding fatty tissue, although sometimes the amount of fatty tissue may be increased. The coronary vessels appear more tortuous than normal and usually there is increased fluid in the pericardial sac.

Quain (1872)[9] reported a series of 171 patients with tuberculosis, in which he found that in 67 per cent of the females and in 53 per cent of the males the heart was small. There was particularly marked reduction in the size of the heart in two patients: an 8 year old girl with a heart weighing 60 grams, and a 14 year old girl with a heart weighing only 82 grams. Audeoud and Jacot-Descombes (1894)[10] quoted Chomel as having reported the case of a man whose heart was no larger than a hen's egg, and cited a case of their own in which the heart weighed only 135 grams. The affected heart may be dark brown in color, owing to accumulation of pigment granules. To this type of atrophy Audeoud and Jacot-Descombes gave the name "brown atrophy" (atrophie brune). They quoted Friedreich, Zielenko, and Goldenberger as having shown that microscopically the fibers of atrophic hearts are smaller than those of the normal heart.

Gibson[1] was the first to mention low blood pressure as part of the clinical picture and observed that in his experience the pericardial sac contained less rather than increased fluid as had been previously claimed.

In the early part of this century the role of inanition in the production of atrophy of the heart was clarified by Voit, 1905,[11] who showed that in starvation in experimental animals the heart loses a significant percentage (16 per cent) of its original weight. Subsequently, evidence was presented indicating that in starvation, heart weight loss occurred in about the same proportion as, or in smaller proportion than, the loss of body weight.[12,17] A survey of the more recent standard textbooks on cardiology and internal medicine revealed that in only three was mention made of this entity.[18,20] Levine and Carr[17] presented the pathologic observations on 10 cases of atrophy. Katz and his collaborators[21] reported 3 patients with brown atrophy associated with electrocardiographic changes, and Willius[22] reported a case of atrophy of the heart in a patient with marked inanition secondary to carcinoma of the stomach and stated that atrophy of the heart is a rare condition.

Recent physiologic studies on convalescence, bed rest and starvation have shown wasting of muscles; decrease in heart size, cardiac output, blood volume, blood pressure, pulse pressure, cardiac reserve, vasomotor tone, and exercise tolerance; and characteristic electrocardiographic changes.[23,43] The reversible nature of atrophy has been illustrated experimentally, and particularly well clinically, by the recovery of inmates of concentration camps after liberation. Blaha[44] reported the high incidence of small hearts and low blood pressure (systolic pressure less than 75 mm. of mercury) among starved prisoners, and recovery by refeeding without apparent residual ill effects.

Incidence

The 85 cases of cardiac atrophy studied represent an incidence of 4.25 per cent; of these, 44, or 2.2 per cent, were brown atrophy, and 41, or 2.05 per cent, simple atrophy. In a

previous series of 2,000 consecutive autopsies by Wartman and Hellerstein[45] at the same institution, only 19 cases of atrophy of the heart were encountered. This higher incidence in our series is probably due to the increasing emphasis and recognition of this entity in recent years.

Predisposing Factors

Age: Table 1 shows the age distribution of the patients with brown and simple atrophy and of the total group. It is significant that patients in the simple atrophy group were twenty years younger than those in the brown atrophy group. This is related to the well established observation[46] that pigment deposition occurs normally with advancing years, and thus appears to be increased relatively when atrophy supervenes in the older patients. Atrophy of the heart predominates in late adult life: 78.8 per cent of our patients were 40 years of age or older, probably because malignant tumors, the most frequent cause of wasting leading to atrophy, are more frequent in the higher decades of life.

Table 1.—*Age Distribution*

Age in Years	Brown Atrophy, Number	Simple Atrophy, Number	Total Group	
			Number	Per Cent
15–19	0	4	4	4.7
20–29	0	4	4	4.7
30–39	1	9	10	11.8
40–49	5	9	14	16.5
50–59	10	10	20	23.5
60–69	17	4	21	24.7
70–79	10	1	11	12.9
80	1	0	1	1.2
Totals	44	41	85	100.0

Average Age

	Years	Range
Brown atrophy group	62	35–82
Simple atrophy group	42	16–76
Total atrophy group	52	16–82

Sex: Table 2 shows the sex distribution and compares the female to male ratio in our series with that found in the total autopsy population at the Institute of Pathology. When the corrected ratio was compared with that of the total autopsy population it was evident that there were three times as many females in our series of patients with atrophy of the heart as would be expected. Thus, there was an absolute and relative predominance of females in the whole group, and a predominance of females in the simple atrophy group as compared with the brown atrophy group. The high incidence of females in the simple atrophy group is probably related to the high incidence of malignant tumors of the reproductive organs among young women (table 3).

Color: Seventy of the patients were white, and 15 were Negro, making a ratio of 4.7:1. There was no significant difference in color distribution when compared to the ratio of 4:1 in the total autopsy population.

Debilitating Diseases: The main pathologic diagnoses are listed in detail in table 3 and summarized in table 4, and demonstrate that atrophy of the heart occurred in conjunction with a variety of diseases, the most important of which were neoplasms (73 per cent or sixty-two of eighty-five cases) and chronic infections (16 per cent or fourteen cases). The common factors predisposing to generalized body and cardiac atrophy will be discussed in detail later.

Table 2.—*Sex Distribution*

	Number		Ratio
	Females	Males	Females to Males
Brown atrophy	21	23	0.91 to 1
Simple atrophy	32	9	3.56 to 1
Total group	53	32	1.66 to 1
Total autopsy population			0.56 to 1
Corrected ratio for total atrophy group			2.95 to 1

Pathologic Anatomy

Criteria for Diagnosis: The diagnosis of atrophy of the heart was made on the basis of the following criteria[47] as evidence of acquired reduction in size of the heart and its fibers: (1) decreased weight, (2) increased pigmentation of muscle fibers, (3) serous atrophy of subepicardial fat, (4) wrinkling of the epicardium, (5) tortuosity of coronary arteries, (6) increase of nuclei: muscle fiber ratio, (7) decrease of muscle fiber size.

In the subsequent discussion, it will be shown that not all of these criteria were required to be present for the diagnosis of atrophy of the heart in each case.

TABLE 3.—Main Pathologic Diagnosis

Diagnosis	Brown Atrophy, Number	Simple Atrophy, Number	Group Total, Number
I. Neoplasm			
A. Benign	2	1	3
Endometriosis	1	0	1
Meningioma	1	0	1
Neurofibromatosis	0	1	1
B. Malignant			
1. Carcinoma	27	19	46
a. Genital			
Breast	2	6	8
Cervix	4	1	5
Ovary	2	1	3
Prostate	1	0	1
Penis	0	1	1
b. Digestive system			
Esophagus	2	0	2
Stomach	5	4	9
Colon	2	1	3
Rectum	3	1	4
Gall bladder	1	0	1
Pancreas	2	0	2
c. Respiratory—Bronchi	3	1	4
d. Nervous system			
Brain	0	1	1
Neuroblastoma (sympathetic)	0	1	1
e. Skin	0	1	1
2. Sarcoma and lymphoblastoma	7	6	13
Lymphosarcoma	2	2	4
Reticular cell sarcoma	2	0	2
Spindle cell sarcoma	0	1	1
Hodgkin's sarcoma	1	3	4
Leukemia	1	0	1
Lymphoblastoma	1	0	1
II. Chronic infection	5	9	14
A. Chronic bronchiectasis and recurrent pneumonitis	2	0	2
B. Tuberculosis, miliary	1	2	3
enteritis	0	2	2
C. Lung abscess	0	1	1
D. Chronic ulcerative colitis	0	2	2
E. CNS syphilis	0	1	1
F. Lymphogranuloma	1	0	1
G. Chronic cholangitis and hepatitis	1	1	2
III. Metabolic disease	0	3	3
A. Addison's disease	0	2	2
B. Cirrhosis	0	1	1
IV. Psychiatric disease	0	2	2
A. Anorexia nervosa	0	1	1
B. Depressed psychosis	0	1	1
V. Others	3	1	4
A. Amyotrophic lateral sclerosis	2	0	2
B. Aplastic anemia	1	0	1
C. Dermatomyositis	0	1	1
Totals	44	41	85

Weight of Heart

There is considerable variation in the accepted range of normal weight of the heart, and of the average heart weight. Röessle and Roulet[48] cite 317 grams for males and 275 grams for females, with an overall average of 296 grams; Cambridge Public Health Service[49] gives 315 to 390 and 220 to 350 grams for the range of males and females respectively. Saphir[50] and the New York Heart Association[20] give an average of 300 grams for males and 250 grams for females.

In our series of patients the range of weight was 99 to 300 grams and the average heart weight was 219 grams (Fig. 1). This latter figure is definitely below any of the accepted normal values. The mean weight of the heart in the brown atrophy group was 231 grams, and in the simple atrophy group 205 grams. The range in the former group was 150 to 300 grams, and in the latter 99 to 250 grams (tables 5, 6). The heavier hearts were found in the brown atrophy group whose members were twenty years older and had heavier and longer

bodies than the members of the simple atrophy group. The average heart weight of the males was greater than that of the females in both groups: in the brown atrophy group the average heart weight of the males was 249 grams, of females 212 grams; in the simple atrophy group the average heart weight of males was 217 grams, and of females 202 grams.

TABLE 4.—*Main Pathologic Diagnosis*

Diagnosis	Brown Atrophy, Number	Simple Atrophy, Number	Total Group, Number
Neoplasm			
Benign	2	1	3
Malignant			
Carcinoma	27	19	46
Sarcoma and lymphoblastoma	7	6	13
Chronic infections	5	9	14
Metabolic diseases	0	3	3
Psychiatric diseases	0	2	2
Others			
Amyotrophic lateral sclerosis	2	0	2
Aplastic anemia	1	0	1
Dermatomyositis	0	1	1
Totals	44	41	85

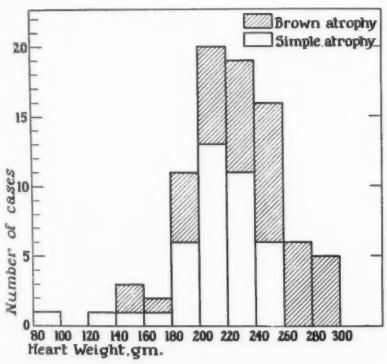

FIG. 1.—Heart weights of eighty-four patients with atrophy of the heart.

Relationship of Heart Weight to Body Weight and to Body Length: The heart size in normal individuals is dependent principally on body build.[59] The combination of weight and height (length) forms an index of body build which, although not completely satisfactory, does allow a correlation with heart size to be made.

Relation of Heart Weight to Body Weight: It has been well established that there is a definite correlation between heart weight and body weight in normal persons. This correlation was thought to be due to the need for a given mass of heart muscle to pump blood to a given mass of tissue.[57] The ratio of heart weight to body weight given by various authors differs considerably.[57] Röessle and Roulet[48] give a range of 0.509 to 0.678 for males from 16 to 76 years old, and 0.407 to 0.670 for females. Greenwood and Brown,[60] Müller,[65] and Scammon[62] give a similar range. Bardeen[63] states that 0.55 per cent of the body weight approximates closely the normal relative proportion of the weight of the heart in males at all ages,

TABLE 5.—*Heart Weight in Eighty-four Patients with Atrophy of the Heart**

	Number Cases	Range of Weight (Gm.)	Mean Weight (Gm.)	Standard Deviation (Gm.)	Standard Error of Mean (Gm.)
Simple atrophy	40	99–250	205	34.6	5.5
Males	9	190–250	217		
Females	31	99–240	202		
Brown atrophy	44	150–300	231	38.7	5.8
Males	23	155–300	249		
Females	21	150–245	212		
Total atrophy group	84	99–300	219	36.5	4.0
Total males	32	155–300	240		
Total females	52	99–245	206		

* The heart weight of one patient was not recorded.

except at birth; in females the relative proportion is about 0.53 per cent of body weight. Boyd[64] gives a higher percentage than do the others: 0.6 to 0.8 per cent.

The New York Heart Association[20] has accepted the ratios of H. L. Smith, i.e., 0.43 per cent for normal males, and 0.40 per cent for normal females. Upon critically reviewing the original thesis, we have found a serious fallacy in the basis from which Smith's ratios were derived. This fallacy, we believe, invalidates the acceptance of his ratio. Smith used the weights of the hearts of patients with carcinoma of the "stomach, breast, colon and sigmoid, tumor of the brain, and peritonitis following operation for lesions of the gall bladder, bowel, prostate,

and kidneys."[57] As indicated previously, numerous experimental studies before and after Smith's report have clearly demonstrated that the heart participates in the generalized atrophy of body inanition and enforced rest.[14, 15] Smith assumed that the above-listed diseases did not affect the size or weight of the heart, and, instead of comparing the weight of the heart with the actual body weight at autopsy, he compared the heart weight with the normal weight of the patient *before* admission to the clinic. Smith admitted that the difference between the weight at entrance and the normal weight was considerable. In cases of malignant tumors, this difference was from 20 to 40 pounds. For this reason, Smith's ratios for normal people are smaller than those of other studies. We are certain that there were many patients with atrophy in Smith's series. Thus, the smallest heart of a female in the adult age group in his study was 110 grams, and of the adult male 155 grams.

TABLE 6.—*Heart Weight and Body Weight and Length in Eighty-five Autopsy Subjects with Atrophy of the Heart*

Simple Atrophy (41 Cases)			Brown Atrophy (44 Cases)		
Heart Weight (Gm.)	Body Weight (Kg.)	Body Length (cm.)	Heart Weight (Gm.)	Body Weight (Kg.)	Body Length (cm.)
230	46	156	180	52	162
210	57	165	290	48	174
240	83	163	195	43	159
190	49	160	245	49	156
120	40	150	230	46	172
240	42	161	291	46	—
250	42	168	275	37	172
190	35	156	240	60	179
220	—	—	260	60	166
230	48	157	260	47	171
200	44	165	170	44	156
190	36	150	244	27	150
240	42	154	240	43	159
240	37	177	250	55	156
220	65	172	280	73	169
207	46	154	276	48	176
220	52	163	276	54	178
180	39	155	215	47	160
204	50	172	230	40	172
145	28	145	230	49	171
—	44	175	240	52	162
200	40	164	260	64	180
185	46	165	280	54	168
220	43	173	226	53	154
210	53	160	225	52	172
200	44	152	195	44	157
180	43	147	200	47	208
220	67	171	240	—	—
240	51	149	250	50	158
215	37	171	150	32	162
200	30	149	190	50	165
230	63	164	155	39	163
210	42	176	250	48	164
200	44	149	210	47	147
200	55	161	220	40	153
200	52	151	200	37	161
220	38	154	230	44	151
99	25	152	195	51	184
170	37	159	230	47	162
220	54	154	300	52	170
220	53	171	200	37	154
			210	52	164
			240	54	168
			210	45	158

The mean body weight of our total group was 47 Kg., with standard deviation of 9.2 and standard error of the mean of 1.02. The members of the brown atrophy group were slightly heavier than those of the simple group; the former had a mean body weight of 48 Kg., with a standard deviation of 8.3 and standard error of the mean of 1.26; the latter had a mean body weight 46.1 Kg., standard deviation of 10.2, and standard error of the mean of 1.63.

In 82 patients whose heart and body weights were recorded in the autopsy protocols there was a definite correlation between body weight and heart weight. The coefficient of correlation, as calculated from the formula

$$r = \frac{\dot{S}X_1X_2}{\sqrt{(SX_1^2)(SX_2^2)}},$$

equals 0.465 for 82 observations. The probability that this correlation occurs by chance is less than 1 to 100.

In table 7 and figures 2, 3, and 4, the heart weight to body weight ratios of 82 patients with atrophy of the heart are presented. The ratio was calculated by dividing the heart weight in grams by the body weight in grams *at autopsy*, and multiplying by 100. The average heart to body weight ratio of the whole group was 0.48. The average ratio of males of the whole group, the brown atrophy group, and the simple atrophy group was higher than that

for females for the same groups (table 7). Also, the average ratio of the brown atrophy group was greater than that of the simple atrophy group, i.e., 0.50 and 0.46 respectively.

In figure 4, the wide scatter of the values of the ratio of heart to body weight in atrophy is apparent. Eighty-seven per cent of our cases fall between 0.35 to 0.60. The figures of Greenwood and Brown[60] are probably representative of the general consensus of the value of the normal ratio and can be used for comparison. These authors found that the heart is approximately 0.575 per cent of the body weight, a value greater than the average of 0.48 for atrophic hearts. Thus, in atrophy of the heart, on the average the heart loses mass to a greater degree than does the body, since the heart weight–body weight ratio is lower than in normal individuals. However, some of our patients had ratios above normal, indicating that the heart had lost less mass than the body. The conclusion that the heart loses mass with the body is in accord with the clinical and pathologic observations of Krieger[12] and of Levine and Carr,[17] and with the results of experimental animal starvation (Simonds and Brandes[16]).

TABLE 7.—*Ratio of Heart Weight to Body Weight*

	Number Cases	Average Heart Weight-Body Weight Ratio	Range of Ratio
Brown atrophy			
Males	23	0.51	0.37–0.77
Females	20	0.49	0.35–0.90
Total brown group	43	0.50	0.35–0.90
Simple atrophy			
Males	9	0.47	0.37–0.59
Females	30	0.46	0.29–0.67
Total simple group	39	0.46	0.29–0.67
Whole atrophy group	82	0.48	0.30–0.90
All males	32	0.50	0.37–0.77
All females	50	0.47	0.30–0.90

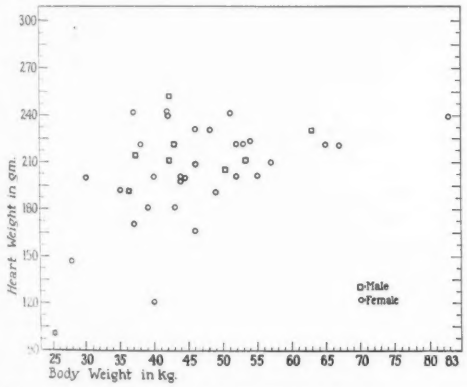

FIG. 2.—Relationship of heart weight to body weight in simple atrophy of the heart.

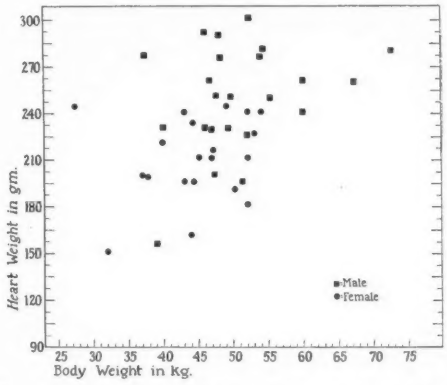

FIG. 3.—Relationship of heart weight to body weight in brown atrophy of the heart.

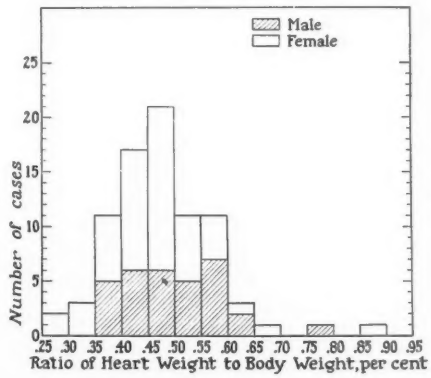

FIG. 4.—Distribution of ratios of heart weight to body weight.

Relation of Body Length to Heart Weight: The mean body length at the time of autopsy for the whole group was 163 cm., with a standard deviation of 10.1 and a standard error of the mean of 1.12. In the simple atrophy group the mean length was 160 cm., with a standard deviation of 9.3 and a standard error of the

mean of 1.5. The mean length in the brown atrophy group was 165 cm., with a standard deviation of 10.8 cm. and a standard error of the mean of 1.7. The higher incidence of men in the brown atrophy group (table 2) may explain the greater body length, since in the general population men are taller than women.

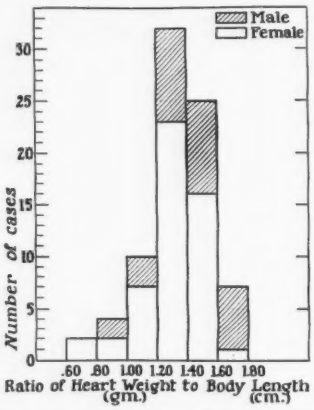

FIG. 5.—Distribution of ratios of heart weight to body length.

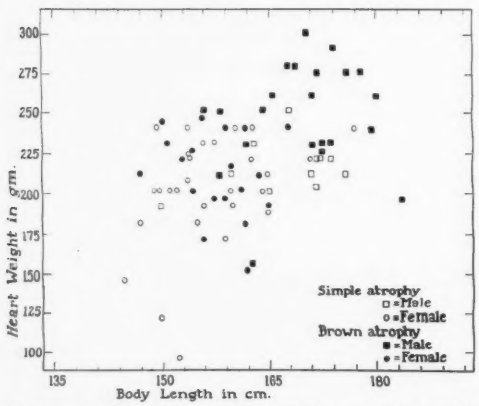

FIG. 6.—Relationship of heart weight to body length.

In figure 5, the distribution of the ratio of heart weight to body length is plotted, with 70 per cent of the cases falling in the zone from 1.20 to 1.60. Since our patients had attained their adult body length before the onset of their illness which produced body and cardiac atrophy, and since body weight and body length are interdependent (Brodie[96]) it is not surprising that there is a significant correlation between heart weight and body length in our cases (fig. 6). The coefficient of correlation, $r = 0.383$ for 81 observations, indicates that this correlation could occur by chance less than once in 100 instances. The higher correlation between heart weight and body weight may be due to a greater loss of body weight than of body length. Although we do not have direct evidence in our cases, it is probable that decrease in body length is mainly due to absorption of cartilage especially in the intervertebral discs.

Myocardium

Gross Description: Color. The myocardium of the hearts with brown atrophy (44 cases) showed a definite relative increase of pigmentation grossly. In the original protocols, the fresh specimens were described as being very pale brown in 3 cases, dark brown in 17 cases, dark reddish-brown in 27 cases, and yellowish-brown in 3 cases. In the simple atrophy group (41 cases) the myocardium had a less intense brown color; in 11 subjects it was described as being pale brown, in 23 reddish brown, in 6 medium brown, and in one yellowish brown. In both groups, generalized icterus was present in those subjects whose myocardium had a yellow hue.

Consistency. The consistency of the fresh specimens varied in each group; in some subjects the myocardium was more flabby and soft than is normal and in others more firm and compact. In the simple atrophy group, 19 specimens were of normal consistency, 11 were softer than is normal, and 11 were firmer. In the brown atrophy group, 10 were of normal consistency, 11 softer than is normal, and 23 firmer. The greater incidence of myocardial fibrosis in the brown atrophy group may explain the firmer consistency manifest in this group.

Thickness of ventricular walls. In table 8 a comparison is made of the thickness of the walls of the left and right ventricles. The wall of the left ventricle was measured 1 to 2 cm. below the auriculoventricular ring of the mitral valve on the lateral border of the left ventricle, and the right ventricle was measured 1 cm. below the pulmonary ring. The thickness of

epicardium, subepicardial fat, endocardium, and columnae carnae was excluded. The average thickness of the right ventricle in 81 subjects was 3.3 millimeters. The range varied from 1 to 6 mm.; in one subject the wall measured 1 mm., in 8, 2 mm. or less, in 2, 5 mm., and one, 6 mm. Measurements in the remaining subjects ranged from 2 to 4 mm. The left ventricle was thicker in the brown than in the simple atrophy group, with an average thickness of 13.1 and 12.1 mm. respectively. The range of thickness of the left ventricular wall in the two groups was similar, from 7 to 19 mm., with an average thickness of 12.6 mm. for both groups. In one patient from both groups the wall measured 19, 16, 8, and 7 mm. and in two subjects it was 9 mm. thick. Measurements in the remainder of the subjects were included in the range of 11 to 14 mm.

TABLE 8.—*Thickness of Right and Left Ventricular Walls in Atrophic Hearts*

	Number Cases	Range (mm.)	Average (mm.)
Right ventricle			
Brown atrophy	41	1.0–6.0	3.2
Simple atrophy	40	2.0–5.0	3.4
Total group	81	1.0–6.0	3.3
Left ventricle			
Brown atrophy	41	8.0–18.0	13.1
Simple atrophy	39	7.0–19.0	12.1
Total group	80	7.0–19.0	12.6

The ratio of the thickness of the left ventricle to that of the right ventricle varied from 11:1 to 2:1. In 3 cases the ratio was 10:5, 8:4, and 7:3. In the remaining cases the ratio ranged from 11:1 to 3:1, with an average of 3.8:1. The patient with a ratio of 7:3 was a 16 year old girl with anorexia nervosa and severe inanition. The electrocardiogram showed a tendency to low voltage, and indicated "right heart strain, or hypertrophy." At autopsy the heart weighed 99 grams. The right ventricle was relatively thick when compared to the left, as indicated by the shift of the ratio. Therefore, atrophy of the left ventricle was greater than that of the right, and thus produced relative right ventricular preponderance, explaining the electrocardiographic findings.[61]

The average thickness of the walls of the right and left ventricles of atrophic hearts is slightly less than that of the average normal hearts studied at the Institute of Pathology, Western Reserve University, or elsewhere,[50] but is within the lower limit of the normal range. In any individual case, the thickness of the ventricular wall is not a measure of the total heart mass. Such measurements are of value only if the capacity of the ventricular cavity is considered.

The capacity of the ventricles was considered to be unchanged or reduced in 73 of 85 subjects. However, in 12 patients (7 with simple and 5 with brown atrophy) there was definite dilatation, most marked in the right ventricle, with thinned walls and flattened columnae carnae and papillary muscles. Similar observations were made by Bertin,[5] and by Bouillaud.[6]

TABLE 9.—*External Measurements of Atrophic Hearts*

Diameter	Number Cases	Range (cm.)	Average (cm.)
Base-apex			
Brown	39	7.0–10.9	8.7
Simple	36	6.5–12.0	8.7
Total	75	6.5–12.0	8.7
Transverse			
Brown	39	7.4–11.5	8.8
Simple	35	5.0–11.0	7.9
Total	74	5.0–11.5	8.3

External heart measurements. The average base to apex, and transverse (base) measurements of the whole atrophy group were 8.7 and 8.3 cm. respectively (table 9). These values are definitely lower than the average normal measurements,[48] and objectively indicate the small size of the atrophic heart.

Microscopic Examination: The microscopic sections of each heart were examined again and our observations were compared with those of the autopsy protocols. There was excellent agreement, so that we believe the following observations are pertinent.

In brown atrophy of the heart, microscopic examination revealed an excess amount of pigment which was golden brown, or golden yel-

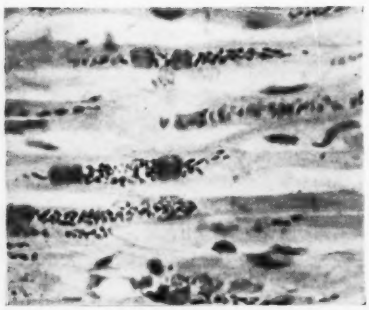

FIG. 7.—Brown atrophy of heart in a 72 year old old white man with carcinoma of the prostate. Blood pressure 110/60. Heart weighed 276 grams, body 48 kilograms. Note increased amount of coarse, roughly rounded pigment granules, for the most part in peripolar position, but also occupying the entire width of myocardial fiber between nuclei. (A 9308.) (Hematoxylin and eosin. × 560.)

FIG. 8.—Simple atrophy of the heart in a 19 year old Negro woman with miliary tuberculosis. Blood pressure 94/62. Heart weighed 200 grams, body 52 kilograms. Note markedly narrowed and twisted muscle fibers, and relative increase of number of myocardial nuclei. Supporting stroma is prominent. (A 9180) (*A*, × 130; *B*, × 560. Hematoxylin and eosin, 8 mm. II Homal, green filter.)

low, in sections stained with hematoxylin and eosin. The pigment was in the form of coarse, roughly rounded granules, varying in size. Characteristically, the pigment granules were located in the sarcoplasm at the poles of the nuclei and frequently occupied the entire region of the myocardial fiber between adjacent nuclei. The latter may represent a more advanced stage of brown pigmentation (fig. 7). In simple atrophy of the heart there was not an increase of peripolar pigment.

The exact source and the composition of the pigment are still undetermined.[51–55] The deposition of brown pigment in the heart begins normally at the end of the first year of life, with a more marked pigment formation after the individual is 45 years of age (Jelinghoff[46]). The pigment has been identified by various workers as lipochrome free from iron,[54] hemosiderin, and hemofuscin and melanin.[53] Similar indecision exists as to whether the increase of brown pigment is relative or absolute in brown atrophy of the heart.

The muscle fibers were arranged compactly in 78 hearts, and loosely, with increased spaces between fibers, in 7 hearts (4 with brown and 3 with simple atrophy). There was a greater predominance of narrow, "attenuated," shorter fibers than is usually found. In 51 hearts (31 with brown, 20 with simple atrophy) the fibers were markedly narrowed and twisted (fig. 8), some resembling the myocardial fibers of the newborn, with few fibers retaining the usually uniform cylindrical shape.[56] However, longitudinal and transverse striations were preserved.

In the above-mentioned 51 hearts with fairly uniformly decreased transverse fiber width, the limit of atrophy may have been attained in a fashion similar to the attainment of maximum transverse diameter in hearts which have hypertrophied (Karsner, Saphir, and Todd[63]). In the remaining 34 hearts (14 with brown, 20 with simple atrophy) the fibers were considered to be within normal limits. There was a variation of fiber width from small to large, with a predominance of fibers of intermediate size. In the entire group of 85 hearts, there was a tendency for more of the small fibers to be

located in subepicardial positions, than in intramural or subendocardial positions.

The nuclei also varied in size and shape. In 33 hearts (20 with brown, 13 with simple atrophy) the nuclei were all smaller than normal. In the remaining hearts there was considerable variation in the same heart in the size of nuclei, some of which were hyperchromatic and no larger than a good-sized lymphocyte, and others large with blunt ends, similar to those found in ventricular hypertrophy. In figure 9, for example, there are large fibers and long broad nuclei with squared ends in a section from the 220 gram heart of a 33 year old normotensive Negro woman who died from neurofibromatosis. In other fields of the same section there were small and medium-sized oval nuclei.

The ratio of the number of nuclei to the number of muscle fibers was estimated by inspection, and was considered to be within normal limits in 45 hearts, slightly to moderately increased in 31, and greatly increased in 6. For a more precise method of evaluating nuclei-fiber ratio the excellent report of Karsner, Saphir, and Todd[68] should be consulted. The increase of the nuclei-fiber ratio was more marked in the brown atrophy group, since 80.5 per cent (33 of 41 hearts) of the simple and 26.7 per cent (12 hearts) of the brown atrophy group were estimated to have normal ratios. In sections of those hearts with increased nuclei-fiber ratios, there was no evidence indicating nuclear mitosis or division. The increase of nuclei is therefore considered to be relative and not absolute. These observations are in accord with those of Karsner, Saphir, and Todd,[68] and likewise confirm the results of Edens[69] who demonstrated an increase of purine nitrogen (nuclear) in atrophy of the heart, indicating a relative increase of nuclear substance.

The exact nature of the process by which myocardial fibers undergo reduction in size is still unknown. Theoretically, atrophic cells should be simply reduced in size. Bradley[90, 91] considers this process to be autolytic, brought about by chemical liquefaction of the tissue proteins, and catalyzed by enzymes present in the cell. The autolytic mechanism has been assumed to explain the atrophic shrinkage of surviving tissue cells, and their return to normal mass again in hypertrophy. The conditions which lead to autolysis and atrophy, and those which favor synthesis and hypertrophy, have been described in detail by Bradley.[91]

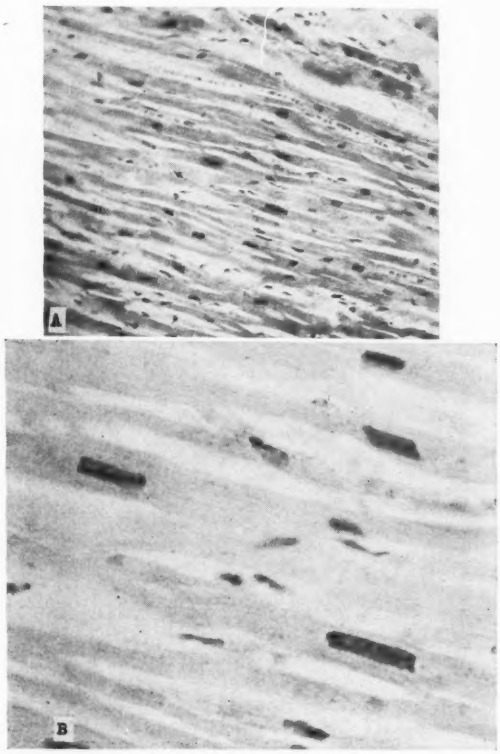

FIG. 9.—Simple atrophy of the heart in a 33 year old Negro woman with multiple neurofibromatosis. Blood pressure gradually fell from 130/80 to 102/70. Heart weighed 220 grams, body 54 kilograms. Note variation in size and shape of nuclei. In center of field there are large blunt nuclei and well developed fibers. (A 9280) (*A*, × 130; *B*, × 560. Hematoxylin and eosin. 8 mm. III Homal, green filter.)

Pericardium

The subepicardial fat varied in amount and nature. In 44 subjects the subepicardial fat was scant or almost entirely absent. In 39 there was an average amount of fat, and in 2 (with simple atrophy) there was an increase of subepicardial fat. In the latter 2 patients the heart and body weights were 220 Gm., 44 Kg., and 220 Gm. and 67 Kg., respectively.

Serous atrophy of subepicardial fat occurred

more frequently in the brown than in the simple atrophy group (17 cases in the brown atrophy and 6 cases in the simple atrophy group). The fat in the auriculoventricular sulci, anterior and posterior interventricular grooves, and over the atria was described as being pale, yellow, or yellowish orange, translucent, watery, gelatinous, or mucoid.

Microscopically, the fat cells were small, and partially collapsed, with discrete or confluent vacuolated spaces at their peripheral boundaries. There was a relative increase of fat cell nuclei per high-power field, and in addition

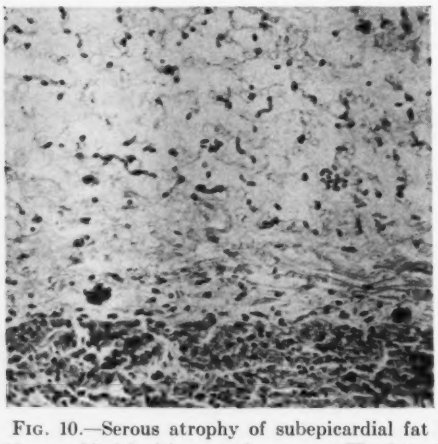

FIG. 10.—Serous atrophy of subepicardial fat in a 16 year old girl with anorexia nervosa. The fat cells are small and partially collapsed, with vacuolated spaces at their peripheral boundaries. The apparent increase of cellularity is due to sparse exudation of lymphoid cells and greater prominence of supporting stroma. A 9214. Heart showed simple atrophy and weighed 99 grams. (A 9214.) (Hematoxylin and eosin. II Homal, green filter. × 80.)

there were scattered exudative cells of the small round cell type with hyperchromatic nuclei, slightly more frequent in perivascular spaces than elsewhere (fig. 10). The apparent increase of cellularity is presumably due to the greater prominence of the supporting stroma and the sparse exudate of lymphoid cells. In 3 patients, subepicardial petechiae occurred, and were probably a terminal event.

Fat infiltration occurred in 12 subjects (8 with simple, 4 with brown atrophy). The range of their heart weights was 200 to 240 Gm., with an average weight of 220 Gm. Although there was evidence of acquired reduction of heart mass, such as wrinkled epicardium, tortuosity of vessels, small fibers, and pigmentation, in 7 subjects there was moderate fat infiltration with local atrophy of the myocardium, in addition to the generalized cardiac atrophy. Fat infiltration was particularly marked over the right ventricle in 6 of 7 patients. Saphir and Corrigan[66] have also noted a similar localization of fat infiltration over the right ventricle.

The epicardium was wrinkled, but smooth, transparent, and glistening in 79 subjects. In 5 there were fibrous adhesions and the visceral and parietal pericardium was slightly thickened. In one patient the sac was obliterated by nonconstrictive fibrous pericarditis. Atrophy of the heart in association with constrictive pericarditis has been attributed to the effect of decreased heart work.[67] In our patient, the pericarditis was nonconstrictive, and the severe inanition secondary to chronic bronchiectasis with recurrent pneumonitis was adequate to account for the atrophy of the heart.

There was a surprisingly low incidence of *hydropericardium* in our series, in view of the reference in the older literature of the association of atrophy of the heart with pericardial effusion. There were 3 patients with 75, 150, and 315 cc. of fluid, respectively, in the pericardial sac.

Coronary Arteries

Increased tortuosity of the coronary arteries is considered as evidence of loss of myocardial mass, without corresponding diminution of the length of the coronary arteries (fig. 11). There was excessive tortuosity in the absence or presence of coronary arteriosclerosis. Extreme tortuosity of the coronary arteries was noted in 30 of 85 subjects, and was twice as common in the brown as in the simple atrophy group. The incidence of moderate to marked coronary arteriosclerosis with stenosis was similarly greater in the brown atrophy group, i.e., 16 cases in the brown and 8 in the simple atrophy group. Likewise, moderate to marked arteriosclerosis of the aorta occurred in 20 patients with brown and 12 with simple atrophy. These findings are

compatible with the older average age of the former group. Increased tortuosity, however, was also noted in the hearts of subjects with simple atrophy with only slight arteriosclerosis (occasional intimal nonstenosing plaques). Two patients had old thrombosis of the anterior branch of the left coronary artery, and old infarcts of the anterior apical left ventricle and interventricular septum. In a third patient a ballooning of the leaflets toward the atria during systole. The competency of the A-V valves under these circumstances is dubious.

Valvular Measurements: In Table 10, the ring circumferences of mitral, aortic, pulmonic, and tricuspid valves are listed. Consistently the average circumference of each valve was greater in the brown atrophy group. The values of the average measurements of the entire group

FIG. 11.—Roentgenogram of atrophic heart (220 gram) injected with barium agar mass. Note the tortuosity of the coronary arteries, and the relative diminution of myocardial shadow. (We are indebted to Dr. A. H. Salans and Miss P. Tweed for this illustration.)

there was a small posterior infarct of the left ventricle and severe coronary arteriosclerosis.

Valves

Valvular structures undergo less shrinkage than does the myocardium in atrophy of the heart. Upon examining an additional 25 atrophic hearts, we have noticed that the valves, especially the tricuspid, appear relatively large in comparison to the mass of the papillary muscles and free walls of the ventricles. The chordae tendineae are long and slack, possibly allowing are within the lower limit of the accepted normal range.[48, 49, 50, 71]

Valvular Disease: The valves were involved by disease in 37.6 per cent (32 subjects). Three patients had chronic deforming rheumatic endocarditis, with stenosis and insufficiency of the mitral and aortic valves in 2 subjects, and mitral insufficiency in one. There were 29 cases of healed nondeforming valvulitis (19 brown, 10 simple). The criteria for the diagnosis of healed nondeforming valvulitis were those presented by Karsner and Koletsky.[70] Qualita-

tively, nondeforming disease of the valves had the same features as those noted in outspoken rheumatic disease. The difference lies in the "fact that quantitatively the various changes have not progressed to a deformity sufficient in degree to alter function."[70] In our subjects, as in those of Karsner and Koletsky, there was polyvalvular involvement, with solitary mitral disease in 5 patients and multiple valvular disease in 24, with the following combinations: mitral and aortic; mitral, aortic, and tricuspid; aortic and tricuspid; and mitral, aortic, tricuspid, and pulmonary valves.

TABLE 10.—*Ring Circumference of Valves of Atrophic Hearts*

	Number Cases	Range (mm.)	Average (mm.)	Normal Range (Rössle and Roulet,[48]) (mm.)
Mitral valve				95.0–125.0
Brown atrophy	43	65–110	93.3	
Simple atrophy	41	66–110	85.9	
Total group	84	65–110	89.7	
Aortic valve				65.0– 95.0
Brown atrophy	43	60– 90	72.6	
Simple atrophy	41	50–100	66.0	
Total group	84	50–100	69.4	
Pulmonic valve				60.0– 80.0
Brown atrophy	44	50–119	74.2	
Simple atrophy	41	45–111	67.9	
Total group	85	45–119	71.2	
Tricuspid valve				110.0–135.0
Brown atrophy	42	82–150	113.9	
Simple atrophy	41	74–135	108.8	
Total group	83	74–150	111.4	

Other Myocardial Lesions

Myocardial Fibrosis: Larger and more areas of myocardial fibrosis were found in the brown than in the simple atrophy group, which is consistent with the older age of members of the former. In the brown atrophy group, there were 23 patients with slight and 11 patients with severe myocardial fibrosis; in the simple group, 21 and 1 patient respectively. Myocardial infarcts occurred in 3 patients—one in the simple and 2 in the brown atrophy group. These infarcts were old, and small. In the remainder of the patients there was no gross or microscopic evidence of fibrosis.

Nonspecific Interstitial Myocarditis: Slight nonspecific interstitial myocarditis occurred in 4 patients, 2 from each group. Two cases were subacute, and 2 chronic. The diagnosis was based upon the presence of diffuse focal infiltration of lymphocytes and monocytes in regions of focal fibrosis.

Degeneration: Moderate cloudy swelling of the myocardium occurred in 4 patients with brown and 2 with simple atrophy. The muscle fibers contained acidophilic granules, many small vacuoles, and indistinct transverse striations. Fatty degeneration occurred in one patient, a 54 year old woman with carcinoma of the breast and widespread metastases. The heart weighed 180 grams and showed simple atrophy. Fragmentation (segmentation) of myocardial fibers was noted in 6 patients with brown and 2 with simple atrophy.

Tumor Involvement of the Heart: The ventricular myocardium was involved, in 2 patients by metastases from an adenocarcinoma of the breast and in one by Hodgkin's sarcoma. The pericardium was involved in 5 subjects, the parietal pericardium in 4, and the epicardium in one. The primary sources included breast, ovary, and Hodgkin's sarcoma.

Atrophy of Other Organs

Atrophy of all organs occurred in varying degrees in our patients with atrophy of the heart. The diagnosis of atrophy was made specifically in the autopsy protocols as follows: liver in 18 cases (6 brown, 12 simple); skeletal muscles, 48 cases; thyroid, 13 cases; pancreas, 9 cases; brain, 6 cases; stomach, 4 cases; kidneys, 4 cases; adrenals, 4 cases; spleen, 3 cases; reproductive organs, 16 cases; and serous atrophy of all body fat in 7 cases. Undoubtedly, the actual incidence was greater than that listed. In table 11, the average weights of various organs are shown to be less than the accepted normal values. In listing the average weights, organs which were the seat of primary or secondary tumor involvement or inflammation were excluded. The lungs were not listed, because of the surprisingly high incidence of significant disease in our series, i.e., 56 of 85 patients. In many patients, multiple pulmonary lesions were present: 46 patients with

bronchopneumonia, 7 with pulmonary tuberculosis, 26 with tumor (22 metastatic, 4 primary), and 8 with pulmonary infarction. The incidence of bronchopneumonia was higher in the brown atrophy group, i.e., 27 cases in the brown and 19 in the simple atrophy group.

Clinical Features

Etiologic Factors

In the preceding section it was shown that atrophy of the heart occurred in association with a variety of diseases and was a part of generalized atrophy of the body. The clinical charts of each patient were reviewed with the purpose of determining the significance of various etiologic factors in the production of this atrophy, such as duration of illness, bedfastness, malnutrition, fever, operative procedures, and radiation therapy. We recognize, of course, that in the final analysis the cause of atrophy is inadequate nutrition, whether primary when there is a decreased utilization of foodstuff by the cells, or secondary when catabolism exceeds anabolism as in overwork or inadequate nutrition (Karsner[76]).

Duration of Illness: Table 12 shows that the duration of illness in the brown and simple atrophy groups is essentially similar. In the total group, only 10 patients were ill for six months or less, 20 for six to twelve months, and the remainder for more than a year. The 10 patients with relatively short illness of six months or less included 5 patients with carcinoma of the gastrointestinal tract (2, esophagus; 2, rectum; 1, stomach), 2 with tuberculosis, 2 with liver disease (hepatitis and cirrhosis), and 1 with carcinoma of the ischiorectal fossa. The 13 patients with illnesses lasting five to

Table 11.—*Weight of Organs in Patients with Atrophy of the Heart*

Organ	Number Cases	Range of Weight (Gm.)	Average Weight	Normal Average Weight (Gm.) (Saphir, [50])
Brain				1275 females, 1400 males
Brown	31	1000–1570	1294	
Simple	26	850–1700	1294	
Total	57	850–1700	1294	
Liver				1500–1800
Brown	31	750–1530	1095	
Simple	29	650–1620	1235	
Total	60	650–1620	1163	
Spleen				150–200
Brown	36	43–400	138	
Simple	33	27–400	140	
Total	69	27–400	139	
Pancreas				90–120
Brown	25	28–120	71	
Simple	24	27–110	64	
Total	49	27–120	68	
Thyroid				
Brown	38	8–63	23	Varies with locale
Simple	35	7–70	21	Less than 40 Gm.
Total	73	7–70	22	
Adrenals (both)				10–12
Brown	41	7–29	14	
Simple	34	5.5–27	15	
Total	75	5.5–29	14	

Table 12.—*Duration of Illness*

Time	Brown Atrophy, Number	Simple Atrophy, Number	Total Group, Number
2–6 months	6	4	10
6–12 months	10	10	20
1–2 years	8	8	16
2–5 years	9	14	23
5–10 years	6	3	9
10–17 years	3	1	4
Unknown	2	1	3
Totals	44	41	85

seventeen years had surgically treated carcinoma of the cervix, ovary, penis, or stomach; chronic ulcerative colitis; depressed psychosis; bronchiectasis with recurrent pneumonia; and frontal meningioma.

Time Bedridden: The duration of time that a patient spends in bed during a protracted illness is probably an important factor in determining the extent of body wasting[33]. In well controlled studies on healthy young men, it was shown that after three weeks of bed rest, there was a decrease of blood volume and heart size, an increase in resting pulse rate, and a decreased capacity to perform a standard amount of work. In these experiments the body weight was kept constant with difficulty. The following metabolic changes have been observed (Dock[29]) consistently in healthy volunteers at complete bed rest: wasting with loss of nitrogen, sulfur, potassium, and phosphorus

TABLE 13.—*Time Bedridden (months)*

	1	2	3	4	5	6	7	8	9	10	60
Brown atrophy cases	12	2	5	6	3	2	2	1	1	1	2
Simple atrophy cases	6	14	7	4	1	1	0	0	0	1	0
Total group	18	16	12	10	4	3	2	1	1	2	2

from the cellular mass of body tissue (Cuthbertson[24]); negative nitrogen balance even with high protein intake; loss of calcium with atrophy of bone; loss of vasomotor tone and decrease of blood volume; and decreased sugar tolerance (Blotner[73]).

In our cases, the clinical charts were reviewed, and an approximate idea of the time of bedfastness was obtained, particularly in those patients with repeated hospitalizations. Many of the patients had been invalided, although not completely bedridden, with marked limitation of physical activity. Adequate data were obtained from the charts of 71 patients, and are presented in table 13. The duration of bedfastness ranged from one month to five years. Fifty-six of 71 patients were bedridden for four months or less, and the remaining 15 patients (3 with simple and 12 with brown atrophy) from five to sixty months. Thus, the duration of bedfastness was longer in the group with brown atrophy of the heart than in the simple atrophy group.

Malnutrition-Inanition: The recent studies of Keys and others[33–41] on human starvation and its consequences indicate anatomic and functional impairment of the circulatory system. Furthermore, it has been long known that the average weight of the heart in emaciated patients is less than that of well nourished patients[14, 15, 72]. With this in mind, we evaluated the nutritional state, extent of body weight loss, and the mechanism of weight loss in our patients with atrophy of the heart.

In describing the *nutritional state* as being defective, we wish to emphasize that there were probably multiple deficiencies, including protein, fat, carbohydrate, and vitamins. The term "nutritional failure" would probably be more apropos, indicating varying degrees of mixed deficiencies existing simultaneously[74]. In our patients, a rough index of the general nutritional state was obtained from the description of the amount and character of subcutaneous fat and skeletal muscle, turgor, and elasticity of the skin. At autopsy, 45 patients were severely emaciated ("skin and bones") (fig. 12), 33 poorly nourished, 6 moderately well nourished, and one was actually obese (table 14). The latter was a 39 year old white woman with Hodgkin's sarcoma, whose weight decreased from 100 to 83 Kg. during the eleven months of her illness. She had been completely invalided during the last three months of life. Her heart weighed 240 grams, and showed simple atrophy. It appears that there were more emaciated patients in the brown than in the simple atrophy group, which may be related to the older age of members of the former group and to the higher incidence of carcinoma in this group (table 4).

During the protracted course of their illnesses, the majority of patients received either therapeutically or prophylactically multivitamin therapy. Doubtless the incidence of avitaminosis was higher than specifically noted in the clinical charts or autopsy protocols. Specific vitamin deficiency was noted in 10 patients only: B complex deficiency in 5, vitamin A deficiency in 2, vitamin K in 2, and multiple vitamin deficiency in one.

Sufficient information was available in the records of 66 patients to determine the *amount of weight loss* during their illnesses (table 15). Body weight loss was obtained by subtracting

Fig. 12.—A 16 year old girl with anorexia nervosa, one day before death. At autopsy the heart weighed 99 grams, and was the seat of simple atrophy.

the body weight at autopsy from the patient's weight at the onset of his illness. The total group lost 25.9 per cent of the body weight with a range of 5 to 60 per cent. The brown atrophy group lost slightly more than the simple atrophy group; 27 per cent and 24 per cent respectively. The range of the brown atrophy group was 10–52 per cent (6 to 58 Kg.), and of the simple atrophy group 5 to 60 per cent (3 to 46 Kg.). In the total group, the men lost 27 per cent of body weight and the women 25 per cent.

In experimental starvation of man,[32,43] diets were designed to cause a loss of 25 per cent of the original body weight in a period of six months. Since our patients with proved atrophy of the heart lost a similar proportion of body weight over a period of months to years, we believe that the experimental subjects also may have developed atrophy of the heart. The similarity of blood pressure changes, roentgenographic studies, and electrocardiograms of our patients with atrophy of the heart and of

TABLE 14.—*Nutritional State at Autopsy*

	Obese	Normal	Poorly Nourished	Emaciated
Brown atrophy	0	2	12	30
Simple atrophy	1	4	21	15
Totals	1	6	33	45

experimentally starved men will be presented subsequently.

In experimental human starvation the *basal metabolic rate decreased* to approximately minus 30 per cent when 25 per cent of the body weight was lost. Although the basal metabolic rate was not determined in our subjects, it is probable that there was a similar decrease. Duncan[97] states that the reduction in metabolism in starvation is proportionately greater than the reduction in body mass. Master[94] has applied the principle of the reduction of metabolism by means of undernutrition, in the therapy of patients with congestive heart failure, angina pectoris, and coronary artery thrombosis.

Although atrophy of the heart occurs as part of generalized body atrophy, large hearts may be found in patients with wasting due to hypermetabolism, as in hyperthyroidism. In experimentally induced hyperthyroidism[16], large hearts were similarly produced, although the animals lost 25 to 35 per cent of their original

TABLE 15.—*Weight Loss during Illness*

Brown Atrophy				Simple Atrophy			
Pre-illness Body Weight (Kg.)	Weight Loss (Kg.)	Per Cent Body Weight Loss	Heart Weight (Gm.)	Pre-illness Body Weight (Kg.)	Weight Loss (Kg.)	Per Cent Body Weight Loss	Heart Weight (Gm.)
Males				Males			
66	6	10	240	61	18	30	220
68	21	31	200	62	9	15	210
50	11	22	155	69	32	46	215
63	16	25	230	60	18	30	210
69	28	40	195	64	10	16	220
64	10	15	276	61	19	31	250
75	27	36	276	50	14	28	190
114	40	35	280	71	21	29	204
76	23	30	250	Females			
60	13	22	260	44	4	10	200
70	10	14	260	57	11	19	185
66	16	24	291	48	10	21	180
70	18	26	230	85	18	21	220
96	36	38	260	63	15	24	240
58	18	31	230	76	46	60	200
66	16	24	230	50	6	12	200
72	14	19	225	65	21	32	200
76	22	29	280	74	22	30	200
75	27	36	250	67	27	40	220
68	16	24	300	40	15	38	99
68	20	29	290	51	14	27	170
Females				57	3	5	220
51	14	27	200	52	6	12	230
46	19	41	244	100	17	17	240
52	8	15	170	55	7	13	190
70	32	40	195	43	3	7	120
56	11	20	210	52	10	19	240
68	14	21	240	55	20	36	190
72	28	39	230	58	10	17	230
45	8	18	200	59	15	25	200
52	9	17	195	51	9	18	240
111	58	52	210	55	18	33	240
				83	18	22	220
				73	21	29	220
				53	13	24	180
				39	9	23	145
Males (average)				Males (average)			
71	19.4	26.6	248	62.3	17.6	28.1	215
Females (average)				Females (average)			
62.3	20.1	29.0	209	59.4	14.4	23.4	201
Total brown group				Total simple group			
68.1	19.6	27.4	231	60.1	15.1	24.5	204
Total atrophy group							
63.9	17.1	25.9	219				

body weight. Apparently, if the activity of the cardiovascular apparatus is kept at a high level, even when the rest of the body is undergoing atrophy, atrophy of the heart will not occur. In a broad sense, our patients with atrophy of the heart had a "disuse atrophy",[7] since the work was so markedly reduced.

As to the *mechanism of weight loss*, defective ingestion was an important factor in producing a deficient nutritional state. Eighty-seven and

one-tenth per cent of the patients in the whole group had pronounced anorexia; 42.4 per cent, prolonged vomiting; 25.8 per cent, diarrhea; and 17.8 per cent obstruction of the gastrointestinal tract. The high incidence of anorexia (87.1 per cent) is significant, indicating that the failure to ingest food was more important in producing starvation than was the failure to utilize it. Parenteral feedings were inadequate to supply the energy requirements in these patients, even though physical activity was limited by their disease. We cannot satisfactorily explain the anorexia, although we can speculate, invoking the factors of prolonged recurrent low-grade fever, effects of radiation, of pain, of postoperative exhaustion, of chronic anemia, of depressed mental states, and the vague effects of metastases on the general state of the patient's well being.

Prolonged low-grade fever occurred in 42.4 per cent of our subjects (36 of 85 patients), for periods ranging from weeks to months. In addition, there was the more marked fever during the terminal part of their illnesses, due in 46 patients to extensive bronchopneumonia. In patients with Hodgkin's disease, tuberculosis, bronchiectasis, and lymphosarcoma, the temperature was more markedly elevated with greater fluctuations over longer periods of time.

In 41.7 per cent (35 of 85 patients) extensive major *surgical prodecures* had been performed. An almost equal number of major operations was performed in both the brown and simple atrophy groups, i.e., 17 and 18 respectively.

Twenty patients (11 with brown and 9 with simple atrophy) had *irradiation therapy* in the course of their illnesses. There was no significant increase in the incidence of brown atrophy in those who received irradiation therapy as there were 11 patients with brown atrophy in the 20 who received irradiation therapy and 33 patients with brown atrophy in the 65 who did not receive this therapy. Our observations are in accord with those of Thibaudeau and Mattick[5], who similarly concluded that the incidence of brown atrophy and the degree of atrophy were not related to irradiation. However, we cannot deny that the results of irradiation therapy did not play some role in the pathogenesis of generalized atrophy and atrophy of the heart, possibly through the production of anorexia and vomiting (irradiation sickness).

Cardiac Status

Size, Activity, and Murmurs: Clinically, on the basis of physical examination and roentgenologic examination of the chest, the hearts were considered of normal size in 78 patients, and judged to be slightly enlarged in 7 patients. Within this group of patients with "normal"-sized hearts, there were 4 subjects whose hearts were remarked to be unusually small, with the left border of cardiac dullness well to the right of the left midclavicular line. A diagnosis of "atrophy" of the heart or "microcardia" was made radiologically in 2 of these patients. In 3 patients the area of cardiac dullness decreased perceptibly during the course of the illness, over a period of seven, twelve, and twenty-four months respectively. In one patient the heart changed from a previously large size (13 cm. to the left of the midsternal line in the fifth intercostal space) to a normal size of 9 cm. The hearts of two other patients were originally within normal limits, and became even smaller. It is interesting that of the 7 patients with clinically "enlarged hearts" 5 were or had been hypertensive, and 2 were normotensive. The individual heart weights at autopsy were 210, 244, 225, 230, 230, 190, and 200 Gm. respectively. The average weight of the hearts of this group was identical with the average weight of those of the entire atrophy group, i.e., 219 Gm. Thus, the apparent increase of heart size was due to dilatation. Of the 4 previously mentioned patients with unusually small hearts, none had hypertension. Their individual heart weights were 155, 190, 220, and 99 Gm., with an average of 166 grams, significantly lower than the average. The precordial activity of the patients in the entire group was decreased, with diminished visible and palpable activity.

The heart sounds were of normal intensity in 66 patients, distant or faint in 18, and in only one patient were the heart sounds loud. The latter had hypertension (185/100) which was maintained throughout his illness. Decrease of intensity of the heart sounds was noted in serial examination in 3 patients over periods of one, three, and six years, respectively. Uniformly,

the quality of the heart sounds was described as being soft, faint, and distant. One patient had tick-tock sounds with a rate of 64 and a small heart.

Murmurs were heard in 25 patients (29.4 per cent). Only 3 of twenty-five patients had organic valvular heart disease, at autopsy; rheumatic mitral stenosis and insufficiency with aortic stenosis in 2 patients, and chronic mitral valvulitis and acute verrucous endocarditis, one patient. The murmurs were typical of the lesions. All but one of the 22 remaining patients had faint, soft, low-pitched blowing early systolic murmurs of short duration, localized to the apical region in 17, and heard over the entire precordium in 4 patients. One patient,

TABLE 16.—*Blood Pressure Changes in Atrophy of the Heart*

	Number Cases	Per Cent
No change in blood pressure	14	
Normotensive	12	
Hypertensive	2	
Changes in blood pressure		
Normotensives	29	
Normal to lower normal level	22	
Normal to hypotensive level	7	
Hypertensives	12	
Hypertensive to normal level	10	
Hypertensive to hypotension	2	
Total	55	
Summary—Significant fall of blood pressure		
Normotensives		70.7
Hypertensives		85.7
Total group		74.5

mentioned above, had an unexplained faint, early, apical diastolic murmur which disappeared when this subject was in the upright position. No valvular lesion was found at autopsy to explain this murmur. Since 14 patients had hemoglobin values of less than 50 per cent, it may be possible to ascribe the murmur to anemia. In the other 8 patients the origin of the murmurs remains unexplained.

The systolic murmurs may be explained on a morphologic basis. The valvular structures do not undergo as much atrophy and shrinkage as does the myocardium, and the chordae tendineae are relatively long and slack. During systole, the A-V valves may possibly balloon toward the atria and, because of the relative length of the chordae tendineae, cause an insufficiency and systolic murmurs.

The possible relationship of healed, nondeforming valvulitis to the presence of the above-noted murmurs was also studied. Healed nondeforming valvulitis occurred in 29 of 85 patients (34.1 per cent), involving the mitral valve alone in 5 patients, and combinations of all four valves in the remaining 24 patients. In 8 of the 22 patients with murmurs there was healed nondeforming valvulitis, which apparently played no role in the genesis of the murmurs, in view of the fact that 21 patients with similar healed nondeforming valvulitis presented no murmurs.

Cardiac Mechanism: Regular sinus rhythm was present in all 85 patients. In 3 patients only were there occasional premature beats. One patient had paroxysmal auricular fibrillation after mastectomy, and conversion to regular sinus rhythm was accomplished through quinidine therapy.

Blood Pressure: There was a definite trend for the blood pressure to fall during the course of the illness in patients with atrophy of the heart. The standards recommended by the New York Heart Association[20] were used to classify the blood pressure (hypertension: over 140 systolic and 90 diastolic; normotension: between 139/89 to 100/60; and hypotension: less than 100/60). Of the total group, 75.3 per cent (64 patients) had normal or low blood pressure, and 24.7 per cent (21 patients) had hypertension. Multiple blood pressure readings before and during illness were available in 55 patients, and indicated a trend of the blood pressure to fall significantly during the illness in 76.4 per cent (41 of 55 patients) (table 16). A persistent fall of 20 mm. Hg diastolic pressure was considered to be a significant change. The two hypertensive patients who sustained their blood pressures are worth noting, in that one had carcinoma of the stomach with metastases, and maintained the blood pressure between 230/140 to 190/140, and the other had multiple pulmonary abscesses and his blood pressure ranged between 150/100 and 185/100. To summarize table 16, 85.7 per cent (12 of 14) of hypertensive patients, and 70.7 per cent (29 of 41) of normotensive patients had significant fall of blood

pressure. The former figure compares most favorably with those presented by advocates of various methods of therapy for hypertension, such as rice diet, sympathetic denervation, and low-salt diet.[18]

There was a definite trend for the *pulse pressure* to become narrow as the blood pressure fell during the course of the illness, similar to the observations in experimental human starvation, and in the concentration camps.[95] The fall in systolic pressure exceeded that of diastolic pressure. In the early clinical course of the disease, the average pulse pressure of the 55 patients with multiple blood pressure readings was 52 mm. Hg, with a range of 26 to 90 mm. The average pulse pressure for the same group in the terminal part of the illness was 41 mm. Hg, with a range of 15 to 78 mm., a drop of 11 mm. Hg in the average pulse pressure. Changes in pulse pressure in 55 patients occurred as follows: 23 had pulse pressure which had not changed significantly (within plus or minus 10 mm. Hg of their previous levels); 27 had fall of pulse pressure of more than 10 mm. Hg with a maximum fall of pulse pressure of 59; only 5 had a widening of pulse pressure of more than 10 mm. Hg, with one patient having a maximum rise of 28 mm. of mercury. The decrease of pulse pressure is believed to be due to decreased systolic discharge, because cardiac output is reduced.

Venous pressures and circulation time studies were made in 2 patients only and the values were normal.

Roentgenographic Studies: Roentgenographic studies of the chest were made in 67 of 85 patients during the terminal part of their illnesses, at which time it is reasonable to believe that atrophy of the heart was present. Seven showed slight cardiac enlargement, and 60 had normal or smaller than normal hearts. The diagnosis of "microcardia" was made by the radiologist in 2 patients. No characteristic configuration of the cardiac silhouette was noted. Actually, the pulmonary conus was enlarged in only one patient.

Various measurements and ratios were calculated to determine whether there was a constant relation between the transverse diameter, or cardiothoracic ratio, and the actual weight of the heart at autopsy, and whether the Ungerleider table applied for obtaining the theoretic transverse diameters of the atrophic heart silhouette for various heights and weights.

Transverse diameters were measured as the sum of the maximal distance of the right border from the midsternal line and of the maximal distance of the left border from the midsternal line. The transverse diameter ranged from 9.5 cm. to 15.5 cm., with 25.6 per cent of the patients having diameters below 11.0 cm., 38.5 per cent between 11.0 to 13.0 cm., and 35.9 per cent between 13.0 to 15.5 cm. The range of transverse diameters of atrophic hearts, thus, is identical with that considered normal.[18]

Equally unsatisfactory as an index of atrophy of the heart was the cardiothoracic ratio (between transverse diameter of the heart and the internal diameter of the thorax). The cardiothoracic ratio ranged from 0.32 to 0.55, with 33.3 per cent from 0.32 to 0.40; 41.5 per cent from 0.41 to 0.50, and 21.6 per cent from 0.51 to 0.55. The normal range is from 0.33 to 0.57.[18] Similarly, there was no apparent correlaton between the heart weight at autopsy and the cardiothoracic ratio. For example, the patient with the smallest cardiothoracic ratio (0.32) had a heart weighing 260 Gm., while another patient with a cardiothoracic ratio of 0.55 had a heart weighing 180 Gm. Still another patient with a cardiothoracic ratio of 0.53 had a heart weighing 300 Gm.

The theoretic transverse diameters of the heart silhouette for various heights and weights were obtained from an Ungerleider table, and a comparison made of the theoretic and actual tranverse diameters. In 13 patients of the 40 whose x-ray films were available, the Ungerleider chart could not be applied because their body weights were below those included in the table. In the remaining 27 patients we found that 52, 67, 70, and 74 per cent had actual transverse diameters which fell within a range of plus or minus 10, 15, 20, and 25 per cent, respectively, of the theoretic transverse diameter. Only 52 per cent (14 patients) fell within the normal range, plus or minus 10 per cent of the theoretic transverse diameter. Thirteen patients fell outside of this range, 11 above and 2 below the upper and lower limits respectively.

Since only 74 per cent fell within plus or minus 25 per cent, it is obvious that in our patients with atrophy of the heart the prediction tables of Ungerleider do not obtain.

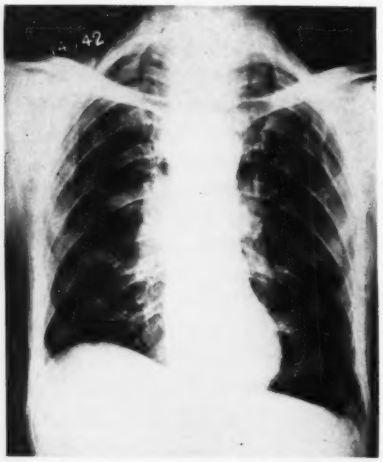

FIG. 13.—Roentgenogram of chest of Patient A 7781, made five days before death. The heart weighed 220 grams and was the seat of simple atrophy.

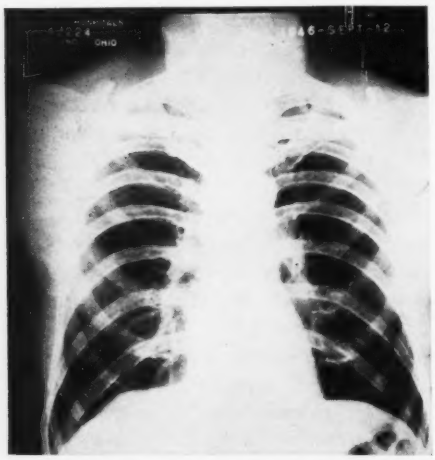

FIG. 14—Roentgenogram of chest of Patient A 9371, made seven weeks before death. The heart weighed 230 grams, and was the seat of brown atrophy.

In summary, the transverse diameters of the atrophic heart by roentgenogram are within the lower part of the normal range (fig. 13, 14, and 15). This is significant, particularly since ordinarily a large percentage of patients in this age group have cardiac enlargement. Because many of the smallest hearts had larger transverse diameters and cardiothoracic ratios than the heavier ones, dilatation must have been present in many instances. In 1833 Bertin[5] recognized clinically that the atrophic heart may be dilated, with thin walls and normal or enlarged chamber capacity.

Clinical Diagnosis of Heart Disease: In none of our patients with proved atrophy of the heart was the clinical diagnosis made ante mortem. The electrocardiogram of one patient was reported as being consistent with the changes found in inanition. In 22 of 85 patients a diagnosis of heart disease had been made at some time in the past or terminal illness—16 in the brown and 6 in the simple atrophy group. The 22 patients had the following diagnoses: 19 hypertensive and arteriosclerotic heart disease, one arteriosclerotic heart disease, one thyrotoxic arteriosclerotic heart disease, and one rheumatic heart disease with hypertension. The patient with thyrotoxic arteriosclerotic heart disease was a 63 year old woman with chronic bronchitis and bronchial asthma, who four years preceding her final admission had auricular fibrillation and hyperthyroidism. After thyroidectomy, the mechanism reverted to regular sinus rhythm. The patient with rheumatic heart

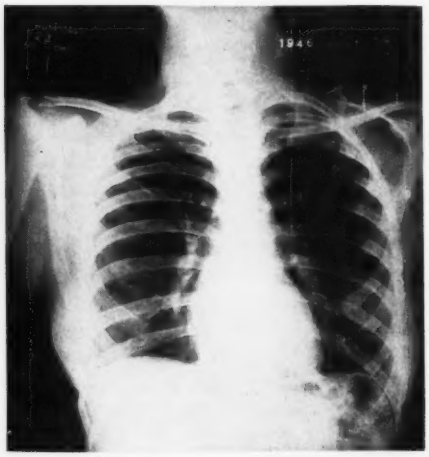

FIG. 15.—Roentgenogram of chest of Patient A 9280, made one month before death. The heart weighed 220 grams, and was the seat of simple atrophy.

disease was a 65 year old woman with bronchogenic carcinoma and aortic and mitral stenosis and insufficiency, with a sustained blood pressure of 160/112. The incidence of arteriosclerotic heart disease was higher in the brown than in the simple atrophy group. The three patients who died with clinically diagnosed heart failure (slight) belonged to the group of 22 patients in whom the clinical diagnosis of heart disease had been made. None of the remaining 63 patients with atrophy died in clinically recognized heart failure.

Clinical Cardiac Competence: The validity of the statement that the atrophic heart is usually adequate to meet the mode of life of the individual—(Karsner[76]) is borne out by the low incidence of clinically diagnosed cardiac decompensation in this series, 3 of 85 patients. Because of the infrequency of clinical heart failure in this series, a summary of the 3 patients is given:

Case 1.—The patient, a 73 year old woman with carcinoma of the ovary and widespread peritoneal and abdominal metastases, was a known hypertensive (blood pressure 180/100) with a history of exertional dyspnea and slight ankle edema for "many years." During the final hospital course the blood pressure fell to 120/85. The heart was enlarged to the anterior axillary line. The electrocardiogram showed left axis deviation, prolonged electrical systole, and occasional premature auricular contractions. There was a systolic murmur at the apex. The patient was transferred to a nursing home with the cardiac diagnosis of hypertensive heart disease, Class II, with cardiac enlargement. A week later she died. At autopsy, in addition to the adenocarcinoma of the ovary, there were passive hyperemia of viscera and arterial and arteriolar nephrosclerosis. The heart weighed 210 grams, and was the seat of brown atrophy. There was acute diffuse myocarditis confined to the right ventricle, cause undetermined.

Comment: From the clinical history and autopsy findings the chronic mild heart failure preceded the clinical onset of carcinoma of the ovary by several years. The clinical impression that the heart was enlarged was undoubtedly due to dilatation, and not hypertrophy. (There was no pneumonitis, or other infection, to which the myocarditis could be related.)

Case 2.—The patient was a 67 year old white man with adenocarcinoma of the rectum with widespread metastases. For six months before admission to the hospital he had a history of mild recurrent dyspnea and ankle edema. During the terminal course he had mild right ventricular failure, which was not considered important clinically. The illness attributable to the carcinoma of the rectum was of one year's duration, and antedated the onset of mild clinical heart failure. At autopsy the heart showed brown atrophy, and weighed 250 grams. There was moderately severe stenosing arteriosclerosis of the coronary arteries, slight nephrosclerosis, and passive hyperemia of the liver.

Case 3.—The patient was a 60 year old white man with amyotrophic lateral sclerosis of four years' duration. On admission to the hospital he had slight ankle edema, his blood pressure was 170/100, and his heart was enlarged to the left. He died two days later, the main cause of death being bilateral bronchopneumonia. At autopsy there was slight passive hyperemia of the viscera, and slight arterial and arteriolar nephrosclerosis. The heart weighed 290 grams, showed brown atrophy, and moderate coronary arteriosclerosis.

Comment: This patient showed clinically mild signs of heart failure, on the basis of hypertensive disease.

The heart failure in the above patients was mild, and was not important clinically. The autopsy protocols were scrutinized with the purpose of discovering whether any other patients had died in heart failure and had been overlooked clinically. In 16 patients, passive hyperemia was found at autopsy, although clinically the diagnosis of heart failure had not been made. Since passive hyperemia is one of the most important sequences of diseases other than heart disease,[76] the records of patients with passive hyperemia were reviewed to ascertain the origin of the process, if possible.

In 5 patients, there was obstruction of the pulmonary artery by emboli, with pulmonary infarction in 4 patients. In addition, there was metastatic involvement of the lungs, liver, adrenal glands, and kidneys, all of which were also the seat of passive hyperemia. It is reasonable to describe this failure as being a terminal event, and secondary to pulmonary artery obstruction. The similarity of symptoms and signs of pulmonary embolism and/or infarction to heart failure has been previously discussed.[77] In one patient there was passive hyperemia of the viscera which could be attributed to the obstruction of the inferior vena cava by metastases of carcinoma of the rectum. In addition there were metastases in the lungs, liver, and

kidney. In the remaining 10 patients, there was passive hyperemia of the lungs, liver, kidneys, spleen, and gastrointestinal tract. Since most of the organs with passive hyperemia were also involved by serious disease, tumors, and infections, we are unable to clarify the exact cause of the passive hyperemia. If we consider the passive hyperemia to be cardiac in origin, the heart failure must have been of a mild, subclinical level, and probably insignificant.

Sudden cardiac insufficiency did not occur in any of our patients with brown or simple atrophy. Fahr[79] reported 2 patients with brown pigmentation of the heart without cachexia who died of cardiac insufficiency during convalescence from a previous illness. It is possible that the hearts were the seat of atrophy and failed because of the increased load imposed during convalescence.[28, 95]

Electrocardiograms: Electrocardiograms of 18 patients were made. In 2 patients, records were made very early in the course of illness (first of thirteen months of illness, and first of an illness of ten years' duration). Their records were normal and have been excluded because it is reasonable to assume that atrophy of the heart had not yet developed. In the remaining 16 patients with tracings made during the middle or late part of the clinical course, the following data were obtained. The constant K was calculated, the formula $K = \frac{QT}{\sqrt{R - R}}$ being used.[81] The amplitude of the QRS complexes and T waves was measured in all leads. For the estimation of the over-all magnitude of the former, the sum of the amplitudes (R plus S) in Leads I, II, and III was obtained. Angle alpha was measured on the Einthoven triangle. Table 17 shows a summary of the electrocardiographic findings.

Interval changes and electrical systole. The Q-T interval was prolonged beyond the upper limit of normal in five patients (B 21, 34, and 42; and S 10 and 27), with K_{QT} ranging from 0.43 to 0.52.

The P-R interval was prolonged in 3 patients, in each 0.22 seconds. The QRS complexes had a mean duration of 0.072 seconds with a standard deviation of 0.011 seconds and standard error of mean of 0.003. The maximum duration was 0.10 seconds, and the minimum was 0.06. In the normal series of Shipley and Halloran,[98] the mean duration was 0.086 seconds. In our series of atrophy of the heart the shorter duration of the QRS complex is significant and indicates a decrease in the time for depolarization of the ventricular myocardium. In hypertrophy on the other hand, the opposite obtains.[81]

Electrical axis. In 11 patients the electrical axis was in the normal zone (0 to 90 degrees); in 4 patients there was a shift of the axis toward the left: −3, −8, −30, −30 (the last two were considered abnormal). One patient had right axis shift with an angle alpha of 97 degrees. In a patient with carcinoma of the breast the electrical axis shifted from 0 to −30 degrees.

Amplitude of complexes. The electrocardiograms of 9 patients showed low voltage of the QRS complexes. Six were abnormally low with a sum total of all deflections of the conventional limb leads of less than 15 millimeters. In 3 additional cases there was a tendency to low voltage with a sum total of 18 mm. each. None of these patients had pericardial effusion. At autopsy, only one patient of this group with low voltage had a pericardial lesion which might account for the low voltage. This patient had fibrous adhesions between the visceral and parietal pericardium, completely obliterating the pericardial sac, but not producing compression. The etiologic basis of the pericarditis was not determined.

The T waves were abnormally low, flat, or negative in 11 of 16 patients. In 6 patients the T waves were isoelectric or negative, and were probably primary T-wave changes. In 2 of 3 patients with multiple tracings the T waves became progressively lower (fig. 16). In one patient, the T waves changed from low amplitude to isoelectric, and in one from isoelectric to negative.

The RS-T segment was abnormal in seven patients, being depressed in Leads II and III in three, and depressed in Leads I and II in four patients. A tentative diagnosis of possible right heart strain was made in Patient S 39, and of left heart strain in Patient B 42.

The P waves were of normal amplitude and duration in 9 patients, of low amplitude in five,

broad in Lead II in one, and peaked and narrow in Leads II and III in one.

The unipolar chest leads also showed low voltage of the QRS complexes and negative or flat T waves in Leads V_1 through V_5 (fig. 17).

Mechanism and rate. The rate ranged from 55 to 130 beats per second, with an average of 92 and a majority below 88. In 3 patients with multiple electrocardiograms, the heart rate progressively decreased, from sinus tachycardia in the early or midportion of the course of illness, to normal rates in the late part of the illness. There were 5 patients with sinus tachycardia (over 110) and 2 patients with sinus bradycardia. The remainder had regular sinus rhythm. Sinus arrhythmia was not present in any of our patients. Paroxysmal auricular fibrillation occurred in one patient, a 58 year old woman, after mastectomy, and was successfully treated with the exhibition of quinidine. An electrocardiogram four months later, a week before death, showed regular sinus rhythm. Premature beats were noted clinically in 3 patients, and electrocardiographically in 2 patients (in one auricular, in the other ventricular).

Our results are consistent in the main with those of Katz, Saphir, and Strauss[21] in 3 cases of brown atrophy of the heart, and of Ellis,[36] Tur,[35] Cardoza and Eggink,[37] Simonson and associates[43] in clinical and experimental inanition. The general observations of decrease of amplitude of QRS complexes and T waves have been noted in famines, and in diseases where there is marked inanition, such as lupus erythematous disseminatus (Liebow and Feil[32]). Sinus bradycardia, however, was not as frequent or as marked in our series. This may be due to the high incidence of fever.

Right axis shift was infrequent in our series. The danger of applying significance to axis "deviation" as an index of ventricular hypertrophy is apparent,[81] in view of the occurrence of abnormal left axis deviation of −30 degrees in patients whose hearts weighed 200 to 240 grams. The high incidence of prolonged electrical systole may be related to hypocalcemia secondary to the negative calcium balance noted in patients and in human experimental subjects after prolonged bed rest and inanition.

In summary, of 16 patients with electrocardiograms made during the mid or late part of their illness, 13 had definitely abnormal records, with main findings of low voltage of the QRS complexes and T waves, and prolongation of electrical systole. Serial records showed progressive diminution of voltage of all complexes, and slowing of rate and prolongation of P-R and Q-T intervals. Duration of QRS complex was in the lower limit of the normal range.

Other Laboratory Studies

Red blood cell counts and hemoglobin determination had been performed on 82 of 85 patients. The other three patients died at home. Sixteen patients had normal values (erythrocyte count of 4.1 millions or above). Sixty-six patients had anemia, of whom 61 had the hypochromic variety and 5 the hyperchromic, with color indices from 1.10 to 1.40. The patients with hyperchromic anemia had liver or stomach involvement—by lymphosarcoma in three patients, cirrhosis in one patient, and metastatic carcinoma in one patient (table 18).

Anemia per se, regardless of the type, is known to produce enlargement of the heart owing to dilatation and at times actually to hypertrophy[33,86]. This process is reversible. As anemia improves, the heart returns to its previous normal size[34]. However, it appears that if anemia is accompanied or produced by debilitating, wasting diseases, such as were present in our series of subjects, atrophy instead of hypertrophy of the heart will ensue. This is well illustrated by the marked atrophy of all organs, including the heart, reported in persons with tropical sprue, in which disease a severe macrocytic anemia, indistinguishable from pernicious anemia, is the main clinical feature[88, 89].

Serum protein determinations were obtained in 31 of 85 patients. Nineteen of 31 patients (61 per cent) had abnormal levels (table 19). In patients with liver involvement by tumor metastases, lymphosarcoma, cirrhosis, and dermatomyositis, there was an absolute increase of globulin above the level of 2.5 Gm. per 100 cc. of blood. Changes in the albumin-globulin ratio occurred in 25 patients, in whom the ratio fell below 1.5:1.

The serum calcium value was determined in

TABLE 17.—*Electrocardiograms of Sixteen Patients With Atrophy of the Heart*

Case Number	Heart Weight (Gm.)	Pathologic Diagnoses	Mechanism	Heart Rate	P-R Interval (Sec.)	QRS Duration (Sec.)	Q-T Interval (Sec.)	K_{QT}	Electrical Axis	Total QRS (mm.)	Limb Leads			Chest Leads	Final Interpretation
											P Wave	T Wave	RST-Segment		
Brown Atrophy Group															
21	240	Aplastic anemia. Fat infiltration of the heart	RSR	115	0.14	0.07	0.36	0.50	30	14	N	Flat	Depressed, in Leads I, II	O	DAC, low voltage, prolonged Q-T interval
27	200	Carcinoma of colon, with metastases	RSR	77	0.16	0.08	0.34	0.39	20	23	N	N	N	N	WNL
31	190	Carcinoma of cervix with metastases	RSR	75	0.19	0.08	0.32	0.36	0	25	N	N	N	N	WNL
32	155	Carcinoma of rectum with metastases	RSR	100	0.12	0.06	0.32	0.41	74	28	N	N	Depressed, in Leads I, II, III	N	Probably WNL
34	210	Sarcoma of stomach with metastases. Fat infiltration of the heart	SB	55	0.16	0.08	0.48	0.46	37	9	L	L	N	L	DAC, Low voltage, prolonged Q-T interval, sinus bradycardia
41	200	Carcinoma of cervix with metastases to left ventricle and interventricular septum	ST	115	0.14	0.08	0.26	0.36	42	32	N	Neg. in Leads I, II	N	L	DAC, T-wave changes may be due to tumor metastases to left ventricle, sinus tachycardia
42	210	Carcinoma of ovary with metastases	RSR PAC	70	0.22	0.06	0.40	0.43	−3	20	L	L	Depressed, in Leads I and CF_4	L	DAC, prolonged Q-T and P-R intervals, left - sided heart "strain"
Simple Atrophy Group															
2	210	Carcinoma of ovary with metastases to parietal pericardium	RSR	100	0.15	0.06	0.31	0.41	40	18	L	Flat, L in Leads I, II Inverted, in Lead III	Depressed, in Leads I, II	O	DAC, tendency to low voltage
10	220	Addison's disease	RSR	100	0.16	0.07	0.40	0.52	12	29	N	Flat, in Leads I, II Inverted, L in Lead III	Depressed, in Leads I, II	L	DAC, prolonged Q-T interval
18	220	Chronic ulcerative colitis	ST	120	0.14	0.05	0.28	0.40	12	18	N	N	N	L	Sinus tachycardia, tendency to low voltage
20	204	Sarcoma of gallbladder. Fat infiltration of heart	RSR	61	0.22	0.08	0.38	0.39	22	18	N	N	N	O	Sinus bradycardia

27	180	Lymphosarcoma record (1)	RSR	100	0.16	0.08	0.35	0.45	−8	18	Broad P_2	L	Depressed, in Leads I, II, III	L	DAC, prolonged Q-T interval, tendency to low voltage
		record (2)	RSR	75	0.22	0.07	0.40	0.45	−4	13	Broad P_2	L			DAC, prolonged Q-T interval, lower voltage than in the first record
30	240	Carcinoma of breast with metastases (1)	AF	130	—	0.07	—	—	0	8	—	L	N	L	DAC, auricular fibrillation, low voltage
		(2)	RSR	88	0.18	0.07	0.34	0.41	−30	8.5	L	L	N	O	DAC, low voltage
32	200	Chronic ulcerative colitis (1)	RSR	130	0.16	0.07	0.24	0.35	−30	11	N	L	N	L	DAC, low voltage
		(2)	RSR (PVC)	75	0.18	0.06	0.30	0.34	*	4	Flat	Flat	N	L	DAC, lower voltage than in the first record
33	240	Nephrosis. Lung abscess	RSR	88	0.13	0.06	0.32	0.41	60	14	L	L	N	L	DAC, low voltage
39	99	Anorexia nervosa	RSR	79	0.20	0.10	0.36	0.42	97	20	Peaked P_2, P_3	Flat, in Lead I Inverted in Leads II, III	Depressed, in Leads II, III	Inverted	DAC, possible right-sided heart "strain"

KEY:

N—Normal.
L—Low voltage.
O—No record.
DAC—Definitely abnormal record.
WNL—Within normal limits.
*—Complexes too low to measure electrical axis.
RSR—Regular sinus rhythm.
SB—Sinus bradycardia.
ST—Sinus tachycardia.
PAC—Premature auricular contractions.
PVC—Premature ventricular contractions.
AF—Auricular fibrillation.

In Patients 27, 30, and 32 of simple atrophy group, record 1 was taken early or in the midcourse of illness, and record 2 in the late part of terminal illness.

7 patients, of whom 5 had values below 9.5 mg. per 100 cc. In these 5 patients, serum protein was 3.95, 4.54, 6.2, 6.2, 6.6, and 8.23 grams per 100 cubic centimeter. Clinical manifestations of hypocalcemia were not noted in any of the above patients. One patient had a serum calcium of 7 Gm./100 cc. and a normal electrocardiogram.

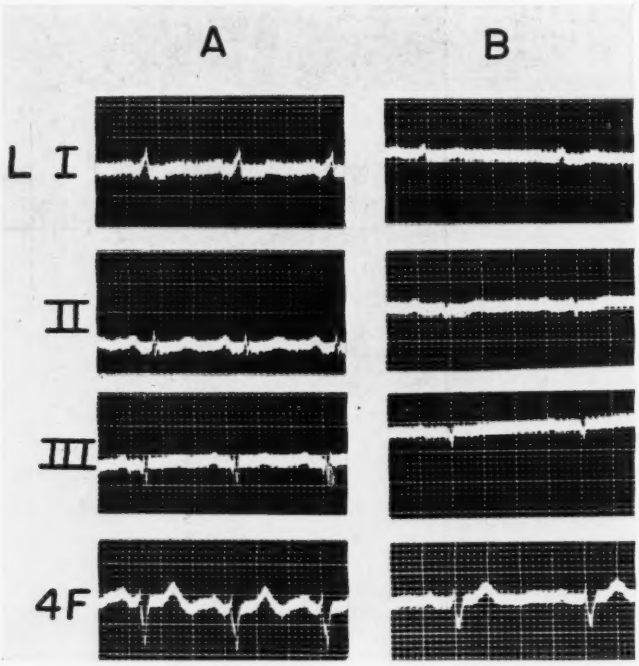

FIG. 16.—Electrocardiograms of a 51 year old white woman with chronic ulcerative colitis, made six months and one month, respectively, before death. There is progressive decrease in amplitude of complexes in all leads, and slowing of rate. The heart weighed 200 grams; the right ventricle measured 3 mm., and left ventricle 12 mm. in thickness.

Clinical Implications.

In experimental inanition, and in experimental prolonged bed rest, the changes in the cardiovascular system resemble remarkably those found in our patients with proved atrophy of the heart. The changes include: small hearts, slow pulse rate, small pulse volume, and decrease of blood volume, blood pressure, cardiac output, basal metabolic rate, and exercise tolerance, and characteristic electrocardiograms. It is reasonable to believe, therefore, that atrophy of the heart was produced experimentally. This atrophy was reversible. In the young experimental subjects, simple atrophy was probably produced, and in older subjects brown atrophy. The weakness or "effort syndrome" which persists for weeks after medical or surgical illnesses may similarly be due to atrophy of the heart.

The low incidence of heart failure in our series is undoubtedly related to (1) the decreased work of the cardiovascular system, and (2) change in myocardial fiber size and capillary-fiber ratio. The loss of body mass and the decreased physical activity associated with prolonged bed rest lowers the energy requirements of the body[40]. The basal metabolism was lowered on an average to −30 per cent in experimental human starvation and in the starvation of war prisoners. Master[94] secured a similar reduction in basal metabolism with benefit to his patients with myocardial infarction.

Since the heart participates in the general atrophy of the body, it is possible to speculate that in starved patients with cardiac hypertrophy the reduction of heart mass results in a diminution of muscle fiber mass to such an extent that the relative blood supply of each fiber is correspondingly improved. Roberts, Wearn, and Badal[78] have shown that in hypertrophic hearts there is an increase in the distance from the center of a given myocardial capillary to the periphery of its region of supply, which is approximately proportional to the degree of cardiac hypertrophy. Thus, a diminution of muscle fiber size would be the equivalent of favoring of the coronary blood supply, with a lesser distance for oxygen to diffuse.

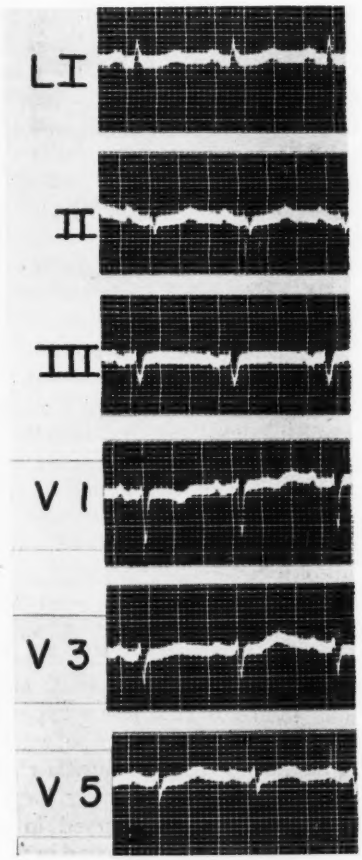

FIG. 17.—Electrocardiogram of a 58 year old white woman with carcinoma simplex of the breast with widespread metastases. Record made seven days before death shows low voltage of all complexes in limb and precordial leads. The heart weighed 240 grams, and the right ventricle measured 4 mm. and the left ventricle 14 mm. in thickness.

Weight reduction has been long known to be one of the few beneficial procedures in the treatment of hypertension. The result of currently popular diets (rice, low-salt, low-protein, low-calory) may in part be due to the absolute weight loss of the body and to a concomitant loss of heart mass with relatively improved capillary-myocardial fiber ratio.

TABLE 18.—*Red Blood Cell Counts in Eighty-two Patients with Atrophy of Heart*

Million R.B.C. per cc.	Number Patients
1.1–2.0	3
2.1–3.0	21
3.1–4.0	42
4.1–above	16
Total	82

TABLE 19.—*Serum Protein in Thirty-one Patients with Atrophy of Heart*

Grams per 100 cc. Serum	Number Patients
Less than 4	1
4.0–4.9	5
5.0–5.9	12
6.0–above	13
Total	31

In general, cardiac patients benefit from reduced metabolism, lowered blood pressure, and a decrease of heart size. Cardiac atrophy by means of a program of undernutrition may be a suitable method for the treatment of selected patients with congestive heart failure, and those with absolute or relative coronary insufficiency with or without hypertension. However, the hazards of starvation and the problems of rehabilitation must be emphasized. After prolonged starvation, heart failure may occur, during the twelve to twenty weeks of rehabilitation, if the metabolic requirements increase more rapidly than the cardiac capacity. Ex-

perimentally, decompensation which occurred during this period was due to the greater circulatory load of increased body activity and increased food ingestion[41]. Hence, if a starvation regimen were applied therapeutically to produce moderate cardiac atrophy, during convalescence, appropriate care should be taken to allow the myocardium fiber mass to increase sufficiently to handle a larger load. The permanency of these gains should be determined by clinical trial.

General summary

Eighty-five cases of atrophy of the heart were encountered in a review of 2,000 consecutive autopsies performed in the Institute of Pathology, Western Reserve University, from 1941 to 1946. Forty-four subjects had excess pigmentation, and 41 had simple atrophy without pigmentation. Atrophy in the former group was called brown atrophy, and in the latter simple atrophy.

Atrophy of the heart predominates in adult life, with 78.8 per cent of our patients being 40 years of age or older. The average of the total group was 52 years, of the brown atrophy group 62 years, and of the simple atrophy group 42 years. The older age of members of the group with brown atrophy is related to the observation that pigment deposition occurs normally with advancing years, and thus when atrophy supervenes in older patients the increase which appears to be absolute may in large part be relative.

Atrophy of the heart occurred in conjunction with a variety of diseases, most important of which were neoplasms (73 per cent, or 62 of 85 patients) and chronic infection (16 per cent). The high incidence of malignant tumors of the female reproductive system probably accounts for the absolute and relative predominance of women in our series.

The diagnosis of atrophy of the heart was based on the following criteria: (1) decreased weight, (2) increased pigmentation of muscle fibers, (3) serous atrophy of subepicardial fat, (4) wrinkling of epicardium, (5) tortuosity of coronary arteries, (6) increase of nuclei-fiber ratio, (7) decrease of muscle fiber width.

The range of heart weight for the entire group was 99 to 300 grams, with a mean of 219 Gm. ±36.5. The mean weight of the brown atrophy group was 231 ± 38.7, and of the simple group 202 ± 34.6. In both groups, the mean heart weight of the males was greater than that of the females, namely, 240 and 206 Gm., respectively.

There was a significant correlation between heart weight and body weight ($r = 0.465$) and between heart weight and body length ($r = 0.383$). The average heart to body weight ratio was 0.48. Since the normal ratio is approximately 0.57, in atrophy of the heart the heart loses mass to a greater degree than does the rest of the body.

Gross and microscopic descriptions of the atrophic heart revealed significant differences between simple and brown atrophy. In the former the color of the myocardium was less intensely brown and the consistency was not as much increased as in the latter. The external measurements, base to apex and transverse diameters and ring circumferences of the mitral, aortic, pulmonic, and tricuspid valves, were all in the lower limit of the normal range. Microscopically, there was an increased amount of golden-brown peripolar pigment in brown atrophy. In some cases the pigment occupied the entire region of muscle fiber between nuclei. In 51 patients the myocardial fibers were markedly narrowed and shortened, although longitudinal and cross striations were preserved. The nuclei varied in size and shape, with an increased number of hyperchromatic shrunken nuclei in both groups. Occasionally, large blunt nuclei, similar to those observed in hypertrophy, and small nuclei were found in the same section. The subepicardial fat was decreased in amount and was the seat of serous atrophy.

The common factors predisposing to generalized body atrophy and therewith heart atrophy were considered to be (1) prolonged illness from two months to seventeen years (2) prolonged bedfastness, and (3) malnutrition producing an average of 26 per cent body weight loss. Defective ingestion of food related to anorexia (87 per cent of patients) was considered the most important factor in producing a deficient nutritional state. Prolonged low-grade fever, repeated operative procedures, and

radiation therapy were considered as being contributory directly or indirectly to the production of body wasting.

Clinical examination revealed small inactive hearts, with normal or faint heart sounds. Murmurs were heard in 25 patients, of whom 3 had rheumatic valvular lesions with typical murmurs. In 21 of the 22 remaining patients the murmurs were systolic, faint, and of short duration, and were heard best at the apex or over the entire precordium. In one patient there was an unexplained diastolic murmur. In 14 patients it may be possible to ascribe the cause of the murmur to anemia, but in the other 8 patients the origin remains obscure.

There was a definite trend for the blood pressure to fall during the course of the illness in which atrophy of the heart developed. Seventy-one per cent of normotensives and 86 per cent of hypertensives had significant falls of blood pressure (diastolic fall of more than 20 mm.Hg.).

The validity of the statement that the atrophic heart is usually adequate to meet the mode of life of the individual was borne out by the low incidence of clinically diagnosed cardiac decompensation in this series (3 of 85 patients).

Roentgenographic examinations of the chest revealed normal or small hearts. Measurements of the transverse diameter of the atrophic heart are within the lower limit of the normal range. The prediction tables of Ungerleider did not obtain in our series.

The electrocardiograms were remarkably similar to those observed in experimental starvation. The significant findings were low voltage of the QRS and T waves, and prolongation of electrical systole and the P-R interval. Serial records showed progressive diminution of voltage of all complexes.

Clinical Implications: The recovery of experimentally starved animals and man, and of inmates of concentration camps, indicates the reversibility of atrophy of the heart and body. The decrease of blood pressure and heart weight of our hypertensive patients indicates that hypertrophy may proceed to atrophy in proper circumstances. Hence, it is conceivable that there are clinical conditions in which it would be desirable to produce slight or moderate body and cardiac atrophy in order to reverse or halt a process of hypertrophy. The production of cardiac atrophy by controlled undernutrition would decrease cardiac work. The permanency of these gains and the problems of rehabilitation should be determined by clinical trial.

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The Failure of Histidine and Vitamin C, and of Ether, to Improve the Peripheral Circulation

Report of Studies on Subjects with Normal Arterial Circulation and with Occlusive Arterial Diseases

By SYDNEY J. WEISMAN, M.D., AND EDGAR V. ALLEN, M.D.

Clinical experience has not confirmed previous observations that intravenous injection of vitamin C and intramuscular injection of histidine monohydrochloride are useful in the treatment of peripheral ischemia observed in arteriosclerosis obliterans. Clinical experience with intravenous injection of ether has failed to indicate that this method of treatment is of value in improving the peripheral arterial circulation in thrombo-angiitis obliterans and arteriosclerosis obliterans.

RECENT studies have indicated that the peripheral arterial circulation of patients with ischemia due to arterial occlusion can be improved as a result of the use of histidine and vitamin C, and as a result of intravenous injection of ether.[1, 2] Because acral ischemia so frequently is resistant to treatment, we have carried out studies to evaluate, critically, these two methods of treatment. In all instances the diagnoses were made by experienced observers*

TREATMENT WITH HISTIDINE AND VITAMIN C

Series A. In 5 cases, arteriosclerosis obliterans was treated with an initial intravenous injection of 500 mg. of vitamin C, followed by subcutaneous injections of 200 mg. of vitamin C and intramuscular injections of 5 cc. of a 4 per cent aqueous solution of histidine monohydrochloride three times daily.†

Case 1.—A man, 63 years of age, was admitted to the hospital because of ischemia of the lower extremities and diabetes. Sudden arterial occlusion of the left popliteal artery had occurred two days previously. The left foot was markedly ischemic and very painful. Three days of treatment failed to relieve pain; signs of ischemia were progressive and amputation was necessary.

Case 2.—A man, 61 years of age, was admitted to the hospital because of arteriosclerosis obliterans; infarction of the right second toe had occurred two weeks previously. Improvement occurred during the first three days in the hospital. At the end of that time the use of histidine and vitamin C was added to the therapeutic program and continued for five days. Healing occurred.

Case 3.—A man, 69 years of age, was admitted to the hospital because of arteriosclerosis obliterans associated with infarcted areas on the right second, third and fifth toes and other signs of marked ischemia. Treatment was carried out for fifteen days but pain and necrosis became increasingly more marked; amputation of the leg was necessary.

Case 4.—A man, 65 years of age, was admitted to the hospital because of arteriosclerosis obliterans associated with marked cyanosis of the right first toe which was moderately painful. Treatment for four days did not produce any change in the objective and subjective evidence of ischemia. The patient left the hospital and returned to his home where amputation was performed subsequently.

Case 5.—A man, 54 years of age, was admitted to the hospital because of arteriosclerosis obliterans, diabetes mellitus, alcoholism and narcotic addiction. There was a deep ulcer measuring 2 cm. in diameter over the right heel, which was extremely painful. Treatment with histidine and vitamin C was carried out for four days without benefit. Other treatment was carried out for an additional two months without benefit. The patient returned to his home but was readmitted to the hospital two months later. The right heel was necrotic and amputation of the leg was necessary.

Summary of Cases Reported in Series A: Observation of the cases reported in this series proves nothing except that very short courses

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* The exact findings and detailed history in individual cases are intentionally omitted from this paper because presentation of them would add unnecessarily to its length. They are recorded in detail in the thesis of one of us (S. J. W.) which was presented to the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, of which this is an abridgment.

† The histidine monohydrochloride and vitamin C were furnished largely by the courtesy of Lakeside Laboratories and Abbott Laboratories.

of treatment with histidine and vitamin C are wholly ineffective in relieving the pain and other manifestations of ischemia in arteriosclerosis obliterans.

Series B. The patients in this series were treated according to the following schedule. An initial intravenous injection of 500 mg. of vitamin C was given and 200 mg. of vitamin C was given orally three times daily. Histidine monohydrochloride in amounts of 5 cc. of a 4 per cent aqueous solution was injected intramuscularly and 100 mg. of vitamin C were injected subcutaneously every four hours during the entire night and day.

Case 6.—A man, 54 years of age, was admitted to the hospital because of diabetes mellitus and arteriosclerosis obliterans. There were ischemic ulcers on the lateral surface of the proximal phalanx of the left fourth toe and on the opposing surface of the left fifth toe, associated with moderate pain. Treatment was carried out for thirty-seven days. There was no change in the appearance of the ulcers and no relief of pain.

Case 7.—A woman, 77 years of age, was admitted to the hospital because of arteriosclerosis obliterans and diabetes mellitus. Amputation of the right leg had been performed four years previously because of gangrene. Pain had begun in the left first toe two months previously and gangrene of the toe had been present for one week. Treatment with histidine and vitamin C was carried out for thirty-eight days; pain increased in severity and necrosis remained unchanged. Amputation of the leg was necessary.

Case 8.—A man, 58 years of age, was admitted to the hospital because of arteriosclerosis obliterans associated with diabetes mellitus. A fracture of the right tibia thirty-five years previously had resulted in adhesion of the skin to the site of the fracture. Massage of this area three months before admission had resulted in a reddened painful area which had been excised. Healing did not occur. On examination, there was, in addition to arterial occlusion and other signs of ischemia, a necrotic ulcer over the midportion of the right tibia. The area was debrided five days after admission to the hospital; a denuded area remained over the tibia which measured 5.5 by 3.6 cm. Treatment with histidine and vitamin C was carried out for thirty-eight days; there was very minor improvement in the appearance of the lesion. The patient returned to his home.

Case 9.—A man, 78 years of age, was admitted to the hospital because of arteriosclerosis obliterans. There was an area of necrosis measuring 2 by 2 cm. over the lateral surface of the distal end of the left fifth metatarsal bone, which was surrounded by an area of inflammation. Pain was mild and was controlled with acetylsalicylic acid and whiskey. The cellulitis disappeared as a result of treatment with penicillin. Treatment with histidine and vitamin C was carried out for nineteen days. Pain became intense and intractable, the gangrenous area progressed in size, and amputation of the leg was necessary.

Case 10.—A man, 60 years of age, was admitted to the hospital because of arteriosclerosis obliterans associated with pain in the left foot (ischemic neuritis) and particularly in the left second toe, on which there had been an ischemic ulcer for six weeks. Pain subsided rapidly and was present in a very minor degree when treatment with histidine and vitamin C was added to the usual program of treatment on the eighth hospital day. It was continued for twenty-nine days. The second toe was amputated near the end of this time because the necrotic lesion extended into the distal interphalangeal joint; healing occurred slowly but was complete.

Summary of Observations of Cases Reported in Series B: It is quite apparent that histidine and vitamin C were valueless in the treatment in the first 4 cases reported in this series. Whether or not they contributed to the good results in the fifth case is a question which cannot be answered. We have repeatedly observed equally good results in instances in which histidine and vitamin C have not been used. Determinations were made of the temperature of the skin of the toes, under basal conditions before and after the courses of treatment. Changes were minor and not indicative of improved circulation as a result of treatment.

Series C. A study was made of the effect on peripheral circulation, as determined by studies of temperatures of skin, of single injections of vitamin C and histidine. Four patients had arteriosclerosis obliterans and 4 patients had normal peripheral arterial circulation. All patients had abstained from the use of food, alcohol, drugs, and tobacco for several hours previously and were at rest in a "constant" environmental temperature which varied a maximum of 0.4 degrees C. during each study period. In all instances but two the environmental temperature was between 25.0 and 26.0 C.; in two instances it was between 24.0 and 25.0 C. The foregoing are considered basal conditions and will be so designated subsequently in this presentation.

Each patient was given 500 mg. of vitamin

C intravenously and rested until the temperature of the skin of the digits had become stabilized. An intramuscular injection of 5 cc. of 4 per cent aqueous solution of histidine monohydrochloride and a subcutaneous injection of 100 mg. of vitamin C were then given and the temperature of the skin was determined at intervals of ten minutes over periods varying from forty minutes to three and a half hours. The original temperature of the skin of the toes in the different studies varied from 24.0 to 29.0 C.; these temperatures easily permit demonstration of arteriolar dilatation. The original temperatures of the skin of the fingers in the different studies varied from 30.0 to 36.0 C. In no instance could it be determined that the injection of histidine causes an increase in blood flow to the digits. Indeed, in a number of instances, the temperature of the skin decreased after injections, and one might conclude, incautiously, that the injection of histidine caused a decrease in the peripheral circulation. Actually the variations in skin temperature were wholly nonspecific and might as well have followed the intramuscular injection of water as of histidine.

Treatment with the Intravenous Injection of Ether

Series D. Diethyl ether was administered as recommended by Katz,[1] except that 25 cc. of ether were added to 500 cc. of an isotonic solution of sodium chloride instead of being added to 1,000 cc. of that solution. The solution of sodium chloride was cooled in the refrigerator for at least twelve hours, and the ether was added immediately before beginning the injection, which occupied approximately one hour. All patients complained of marked burning along the course of the vein during the first few minutes of the injection. Because of local and systemic discomfort, none of the patients permitted twenty-four daily injections, as recommended by Katz.

Case 6.—The patient had been treated previously in Series B. Ether was injected daily for nine days, during the first six of which the patient noted relief of pain for periods varying from five to fifteen hours. During the last three days he did not note relief from the injection and on the ninth day of injection he commented that the pain was the worst it had been since he had been in the hospital. The appearance of the ulcer remained unchanged. Amputation of the leg was necessary.

Case 11.—A man, 42 years of age, was admitted to the hospital because of thromboangiitis obliterans. Amputation of the right leg below the knee had been performed four years previously and there had been recurrent superficial phlebitis of the left leg and infarction of the left second toe for three months prior to admission. Marked ischemia of the left foot was evident and there was early gangrene of the left second toe associated with severe pain. Ether was injected on three successive days without relief of pain. Lumbar sympathectomy was then performed and was followed by gradual relief of pain; restoration of circulation to the toe occurred gradually.

Case 12.—A man, 45 years of age, was admitted to the hospital because of arteriosclerosis obliterans. Ischemic neuritis, characterized by severe burning pain, had affected the right foot for four months. An ischemic ulcer had been present in the midportion of the right anterior tibial area for one month. Sympathectomy performed prior to admission had been without benefit. Ether was injected daily for three days; the pain was not lessened and the patient requested discontinuation of the injections because of inebriation which he found to be distressing. It was apparent that nothing could be accomplished by medical treatment and amputation was advised; the patient returned to his home.

Case 13.—A man, 38 years of age, was admitted to the hospital because of thromboangiitis obliterans. Operative procedures prior to admission had consisted in bilateral lumbar sympathectomy, five years previously, and amputation of the left leg, two years previously. For three months he had had an extremely painful ulcer on the right first toe. He had continued to smoke. Ether was injected daily for six consecutive days. Pain was not relieved and the patient refused additional injections. After several weeks of treatment, pain was relieved and the ulcer healed.

Case 14.—A man, 58 years of age, was admitted to the hospital because of arteriosclerosis obliterans, diabetes mellitus, and an ischemic ulcer over the left medial malleolus. Ether was injected daily for six days; the patient refused further injections because severe nausea and vomiting followed two injections. Treatment without ether was continued for three additional weeks, at the end of which time the ulcer had healed.

Case 15.—A man, 57 years of age, was admitted to the hospital because of arteriosclerosis obliterans. For two months, pain in the right foot had been severe. Treatment with histidine and vitamin C for twenty-one days prior to admission had not caused lessening of the pain. Ether was injected daily for seven days, during which there was gradual lessening of the pain until it was about a half that which had been present on admission. For three days

the patient did not receive ether; seven more daily injections were then given. During the period of treatment, the right foot became progressively colder and an area of gangrene appeared on the right first toe. Pain recurred; the gangrenous area extended; there were other signs of extreme ischemia and amputation of the leg was performed.

Summary of Observations of Cases Reported in Series D: There was nothing in observation of any of these cases to indicate that the intravenous injection of ether was beneficial. Failure of relief of pain was striking. There was no clinical evidence of improvement in arterial circulation which could be attributed directly to the intravenous injection of ether. To be sure, the number of injections was small in most instances but, in general, the patients did not desire further injection, a reaction which lends strong support to our own clinical observations that the injections were largely or wholly without value.

Series E. In nine instances, studies of the temperature of the skin of the digits were made under basal conditions to determine the effect of a single injection of ether on blood flow to the digits. Three of these cases have been previously recorded as Cases 11, 12, and 14. In 2 of these cases (11 and 12) there was no increase in the temperature of the skin as a result of the injection. In Case 12 there was a minor increase in the temperature of the toes during the injection of ether.

Case 16.—A man, 58 years of age, was admitted to the hospital because of diabetes mellitus and arteriosclerosis obliterans with ischemic neuritis of the right foot of four months' duration. During a single intravenous injection of ether, under basal conditions, there was no change in the temperature of the skin of the markedly ischemic right foot but the temperature of the skin of the left foot increased by as much as 4 degrees C. and persisted for an hour after the infusion was terminated. However, when the patient was moved into a room the temperature of which was 32 to 33 C., there was even greater increase in the temperature of the digits of the left foot.

Case 17.—A man, 36 years of age, was admitted to the hospital because of thromboangiitis obliterans. The left first toe had been persistently red for one month and there was a small ulcer on its medial aspect. During the injection of ether the temperature of the skin of the right toes increased 7 to 8 degrees C.; the temperature of the skin of the left toes remained unchanged.

Case 18.—A man, 43 years of age, was admitted to the hospital because of thromboangiitis obliterans. Bilateral lumbar sympathectomy had been performed twenty-six years previously. Seventeen months before admission to the hospital, an ulcer appeared on the left fourth toe; five months before admission, an ulcer appeared on the left first toe after trivial trauma. Prior to admission the patient had received injections of histidine and vitamin C two or three times weekly for seven weeks; no benefit had been apparent. During injection of ether, under basal conditions, the temperature of the skin of the left toes increased about 2.5 degrees C.; no significant change occurred in the temperature of the skin of the right toes.

Case 19.—A man, 22 years of age, without evidence of impaired arterial circulation, received an injection of ether under basal conditions. The temperature of the skin of the toes did not increase above that of the environment (25.0 to 26.0 C.).

Case 20.—A man, 20 years of age, without evidence of impaired arterial circulation, received an injection of ether under basal conditions. During the injection, the temperature of the skin of the toes decreased steadily to that of the environment (25.0 to 26.0 C.).

Case 21.—A woman, 20 years of age, whose peripheral circulation was normal, was given an injection of ether under basal conditions. There was a gradual decrease in the temperature of the skin of the toes.

Summary of Observations of Cases Reported in Series E: These studies of the effect on the temperature of the skin of single injections of ether demonstrate clearly in nine instances that ether injected intravenously does not improve the peripheral arterial circulation except in an occasional case. If ether injected intravenously were an effective and unquestionable method of improving the arterial circulation, it would cause, in each instance, an increase in the temperature of the skin, inasmuch as improvement in the arterial circulation to digits is invariably associated with an increase in the temperature of the skin. In the 9 cases reported in this series, the evidence that ether injected intravenously caused lessening of the peripheral arterial circulation was as strong as the evidence that the procedure caused improvement in the peripheral arterial circulation. The conclusion is inescapable: viewed most optimistically, ether, when injected according to the technic previously described, has little or no value in improving the peripheral

arterial circulation even in subjects whose peripheral arterial circulation is normal and is, therefore, easily increased by such simple measures as a warm environment or the ingestion of alcohol. Indeed, some of the studies are reminiscent of those of the effect of tobacco smoke, which causes impairment of the peripheral arterial circulation.

Conclusions

1. An intravenous injection of 500 mg. of vitamin C followed after an interval by an intramuscular injection of 5 cc. of a 4 per cent aqueous solution of histidine monohydrochloride and a subcutaneous injection of 100 mg. of vitamin C did not cause an increase in digital blood flow as measured by determination of temperature of the skin. Our clinical experience has not confirmed other observations that these agents are useful in the treatment of peripheral ischemia observed in arteriosclerosis obliterans.

2. The intravenous injection of ether had no consistent effect on acral blood flow as measured by the temperature of the skin. In some instances there was evidence of increased blood flow; in other instances there was evidence of a decrease in the acral blood flow. Our clinical experience with the intravenous injection of ether does not indicate that this method is of value in the treatment of ischemia of the extremities in thromboangiitis obliterans and arteriosclerosis obliterans. We were unable to confirm the observations of good results which have been reported previously. Because of unpleasant effects, there was great resistance to repeated injections; some patients refused them. In general, the pain of ischemia was not relieved and there was no improvement in ischemic lesions.

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Ballistocardiographic Findings in Patients with Symptoms of Angina Pectoris

By HERBERT R. BROWN, JR., M.D., MARVIN J. HOFFMAN, M.D., AND VINCENT DE LALLA, JR., M.D.

The physiologic evaluation of the heart by recording mechanical heart actions which in turn are imparted to the body is an approach easily available through the use of the ballistocardiograph. This instrument thus affords a physiologic approach to the problem of angina pectoris and may be used as a diagnostic agent. Ballistocardiographic tracings have been correlated with the histories, physical findings, and electrocardiograms of 50 patients with symptoms of angina pectoris. These were grouped into typical and atypical cases with further subdivision based upon the presence or absence of objective cardiac abnormality. Most significant in the series was the establishment of a definite correlation between abnormality of the ballistocardiographic pattern and the typical cases of angina pectoris. Such a relationship validates use of this instrument as a diagnostic agent in the atypical cases of angina pectoris where it is anticipated that diagnosis can be specifically aided by supplying empiric evidence of cardiac abnormality.

THE diagnosis of angina pectoris is often difficult because of the lack of objective criteria, particularly when the complaints are atypical, for the patient's history is still all important. The purpose of this article is to present the use of the ballistocardiogram as an agent to aid in the diagnosis of angina pectoris.

Angina pectoris is a clinical syndrome of physiologic significance, associated with many conditions, and generally regarded as indicative of myocardial anoxia.[1] It should be emphasized that while coronary arteriosclerosis is the pathologic basis of angina pectoris in approximately 90 per cent of the cases, the terms are not synonymous, and that a careful search should be made for other possible mechanisms.

When the typical symptom complex presents itself the diagnosis of angina pectoris is not difficult. Heberden's[2] original description still is classic. White[3] defines angina as a "retrosternal discomfort, generally a feeling of oppression or weight, characteristically appearing for the first time on ordinary effort, particularly on walking upgrade or hurriedly after meals and in cold weather, lasting a few minutes and subsiding quickly on rest or following use of nitrites. It may radiate to one arm (usually the left) or to both; rarely it begins in the arm."

The history, however, is too often atypical, and in the final analysis one can only question the presence of coronary artery disease. It is also recognized that moderate coronary sclerosis can exist without signs or symptoms. Accordingly the importance of a physiologic analysis of the symptoms becomes apparent.

Numerous procedures have been proposed over the years to aid in the diagnosis of angina pectoris. They include the reproduction of pain by the injection of 1.0 cc. of 1:1000 dilution of epinephrine[4]; a standard exercise-tolerance test in which pain is brought on by exertion[5]; the effect of the external application of heat and cold[6]; the demonstration of a hyperactive cardioinhibitory carotid sinus reflex[7]; the production of the anginal syndrome by inducing general anoxemia[8]; and the observation of electrocardiographic changes during attacks of angina pectoris as compared with those when free from pain.[9] Persistent electrocardiographic abnormalities are usually regarded as significant, but often there are no objective diagnostic findings. Also electrocardiographic changes which are often considered to be associated with angina pectoris may be caused by many other conditions.[10] The above measures give evidence to the continuing search for objective aids to supplement the patient's history.

A new approach to this problem has been

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made possible by the ballistocardiograph. This instrument affords a physiologic approach to a physiologic problem, for it records mechanical heart action. This action may be estimated by analysis of the amplitude, regularity, and definitiveness of the various wave patterns of the ballistocardiogram. Briefly, these waves arise from the heart beat itself and when the pulse impact of the ejected blood strikes the arch of the aorta, pulmonary arteries, and the peripheral vessels.

In an attempt to correlate the ballistocardiogram with the symptoms of angina pectoris, the logical approach seemed to be based upon a careful grouping of the patients. If a definite relationship could be established between the mechanical action of the heart and the symptoms in patients with angina pectoris in whom the diagnosis is beyond question, then the instrument should be of value in aiding the physician when the diagnosis is less certain.

The cases were divided into two major groups, the typical cases of angina pectoris and the atypical cases. The specific groups and their classification are as follows:

Group I. Typical cases of angina pectoris
- *A.* Without objective evidence of cardiac abnormality
- *B.* With objective evidence of cardiac abnormality

Group II. Atypical cases of angina pectoris
- *A.* Without objective evidence of cardiac abnormality
- *B.* With objective evidence of cardiac abnormality.

The typical case embraces the following well known symptom complex: (1) Retrosternal or precordial discomfort of a few minutes' duration (2) The discomfort may be with or without radiation, typically to left side of the neck, left shoulder and down the inner aspect of the left arm, but subject to variation. (3) The pain is characteristically produced by effort, sudden exposure to cold, emotional factors, and occasionally after large meals. (4) The pain is typically relieved by rest and nitrites.

The objective evidences of cardiac abnormality include electrocardiographic changes, cardiac enlargement, heart murmurs, congestive heart failure, or a good history of such changes in the past. Patients with a history of acute coronary insufficiency have been included in Group I, B. These patients have the typical symptoms but in addition their history contains one or more episodes of severe cardiac pain which may be of greater duration than the typical anginal attack but without acute myocardial infarction. This type of case has recently been designated as coronary failure, a syndrome of cardiac pain intermediate between angina pectoris and acute myocardial infarction.[11] Presumably the underlying physiopathologic mechanism of these attacks of pain is prolonged, but reversible myocardial ischemia. Five cases of coronary thrombosis with myocardial infarction have also been included in this group. In these cases the diagnosis was substantiated by the accepted clinical findings as well as the typical electrocardiographic changes exhibiting acute myocardial injury.

Group II contained the large number of cases in which the evaluation of the cardiac status was difficult because of the atypical complaints. These cases represent a diversified group; atypical because of the location of symptoms (e.g., epigastric, subscapular); atypical because of an indefinite relationship to the usual causative factors; atypical in that the predominant symptoms may be dyspnea, palpitation, fatigue; or atypical in that the discomfort may persist for more than the usual few minutes although mild and not incapacitating. It is anticipated that the ballistocardiograph will lend diagnostic evidence in an atypical group such as this through the recording of mechanical heart function.

Patients with histories of related cardiovascular disease (e.g., rheumatic heart disease, hypertension) were eliminated from this series. This was done in order to avoid errors in analyzing ballistocardiographic tracings since it is known that such lesions are often associated with myocardial dysfunction.

Patients with pain, with evidence of aortic stenosis, aortic regurgitation, hypothyroidism, hyperthyroidism, acute or chronic pulmonary disease, and the arrhythmias were excluded in this series, as were also those patients with anemia and positive reactions for syphilis.

Method

Simultaneous tracings of the ballistocardiogram, electrocardiogram, and respirations were photographically recorded using the electronic apparatus described by Brown and Pearson.[13] This is a simple brief procedure without discomfort to the patient.

Normal Tracing: The normal tracing is classified 0. Figure 1 shows the waves as named by Starr.[12] Starr[12] in the normal records or those with only slight deviations. The estimation of the relative cardiac output may be made by measuring the amplitude of the I-J complex and comparing it to the base-line shift after standardizing the apparatus.

4. Respiratory Variation: There are normally present larger complexes during inspiration and smaller complexes during expiration. It is generally noted that the expiratory phase of the respiratory

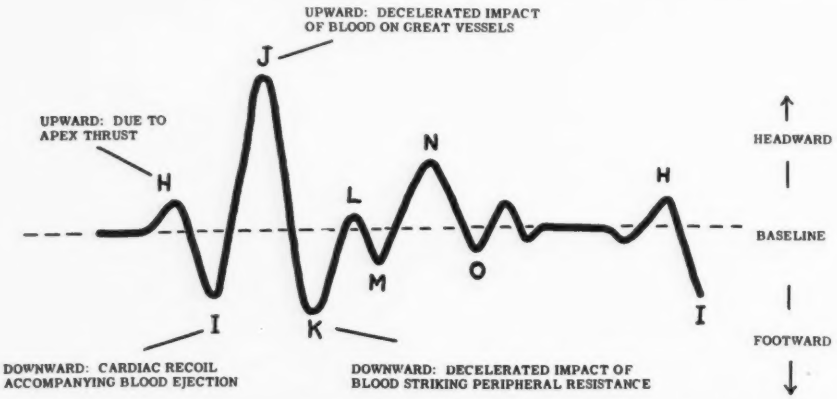

Fig. 1.—A drawing of the normal ballistocardiographic wave pattern with a brief explanation of the most important waves.

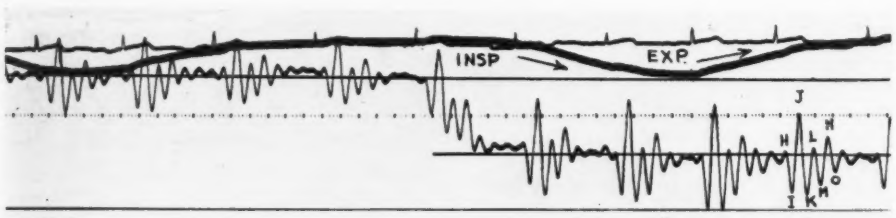

Fig. 2.—Normal Ballistocardiogram. This and the following records show simultaneous tracings of the ballistocardiogram, the electrocardiogram, respirations, and the time line. The heavy undulating line at the top denotes respirations with the downward deflection inspiration and the upward deflection expiration. The distance between the time lines is 0.04 second and that between the two heavy lines 0.2 second.

The analysis of the records to be presented are made by us in the following manner:

1. Regularity of Pattern: The repetition of identical waves occur in the normal pattern with but minor variations between inspiration and expiration.

2. Definitiveness: This constitutes the ability to distinguish the various waves in a complex. This can always be done in the normal pattern.

3. Amplitude: The amplitude of the I-J stroke is believed significant in relation to the cardiac output. The relative cardiac output can accordingly be calculated by means of the formula derived by

cycle constitutes about two-thirds of the time involved (fig. 2). In order to express (for comparison) the degree of variation between inspiration and expiration the respiratory variation index (R.V.I.) is computed from the minute volumes (M.V.).[14]

$$\text{R. V. I.} = \frac{\text{(Largest Inspiratory M. V.)} - \text{(Smallest Expiratory M. V.)}}{\text{Surface Area in Square Meters}}$$

The normals are found to have a R.V.I. between 0 and 450.0 cc. per minute per square meter body

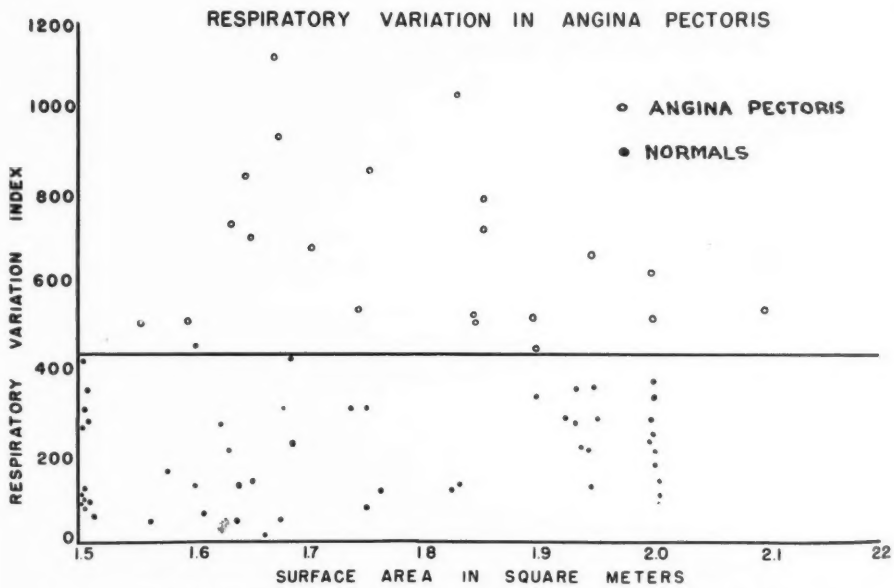

FIG. 3.—A graph of the respiratory variation index against the surface area. A respiratory variation index of 450 cc. was arbitrarily taken as the upper limit of normal since all but one of the 50 normals shown above fell below this line. By contrast those patients with angina pectoris whose relative cardiac output was still adequate (abnormal ballistocardiograms, Grades 1 and 2) uniformly had respiratory variation indices above 450.

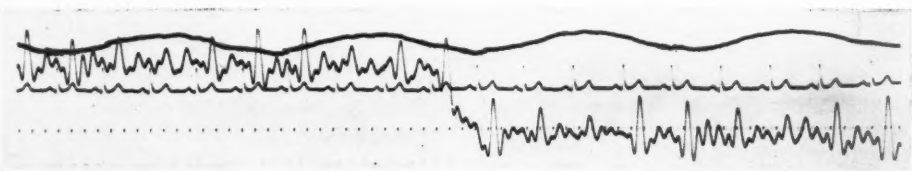

FIG. 4.—Abnormal B.C.G., Grade 1

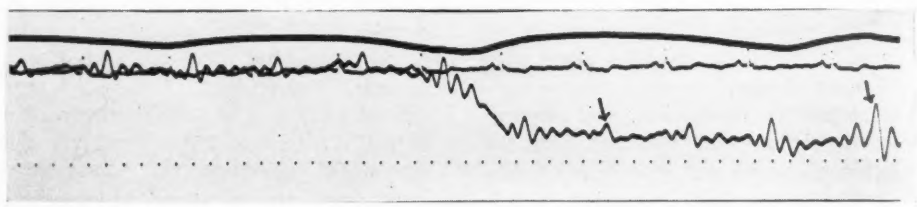

FIG. 5.—Abnormal B.C.G., Grade 2

surface area. Any variation above 450 cc. was considered abnormal (fig. 3).

Classification of the Abnormal Ballistocardiogram: The following arbitrary grades of abnormality have been employed by us to classify conveniently the ballistocardiograms.

0 = Normal tracing (fig. 2).

Grade 1.: The regularity and definitiveness are preserved. The inspiratory I-J amplitude is normal for the minute volume. The expiratory complexes vary, however, in that there is an abnormally decreased amplitude of the waves, and the complexes

usually vary in definitiveness. This accounts for the increased R.V.I. (fig. 4).

Grade 2: One-half or more of the complexes are abnormal, again mainly during expiration. The minute volume in this group is usually decreased owing to a corresponding decrease in the amplitude of the inspiratory complexes as well (fig. 5).

Grade 3: The complexes both in inspiration and expiration show varying degrees of abnormality in regularity and definitiveness. The complexes are still individually identifiable. The amplitude of all complexes is low (fig. 6).

tocardiogram showed varying degrees of abnormality.

Group I, *A* (Table 1) represents 5 patients in whom the diagnosis was made entirely upon the typical symptom complex. There were no objective cardiac abnormalities. The ballistocardiogram was classified as abnormal in each of these cases.

Group I, *B* consists of 21 cases of typical angina pectoris of varying severity with one or

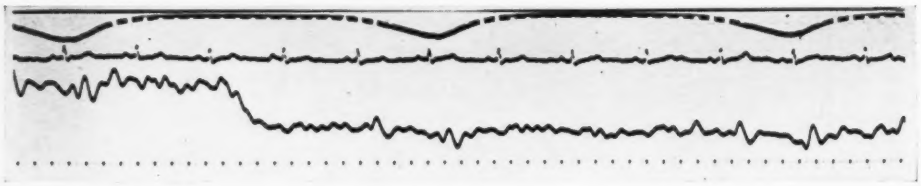

FIG. 6.—Abnormal B.C.G., Grade 3

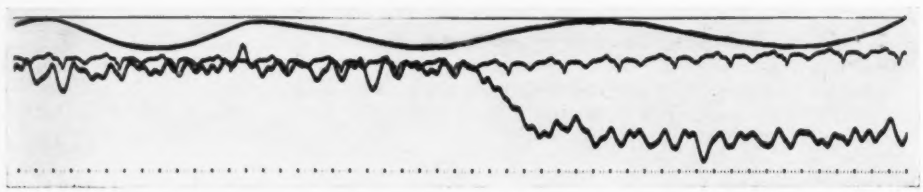

FIG. 7.—Abnormal B.C.G., Grade 4

Grade 4: Totally abnormal complexes are present throughout in this group. They are of low amplitude and are unidentifiable (fig. 7).

DISCUSSION

In this series of 50 patients, 76 per cent were men at an average age of 54 years; and 86 per cent of the members of the entire group were over 45 years of age.

The cardiac symptomatology and physical findings, the electrocardiogram, and the types of ballistocardiograms are presented in tables 1–4.

The main purpose of the paper is to determine any relationship between mechanical heart action as revealed by the ballistocardiogram and the occurrence of the symptoms of angina pectoris. In all of the 26 patients classified as having typical angina pectoris the ballis-

more positive diagnostic criteria of cardiac abnormality. The question logically arises concerning the correlation between the severity of the disease process and the degree of abnormality of the ballistocardiogram. It seems generally true that such is the case. Table 5 reveals that 5 of the patients had a history of acute myocardial infarction and 8 of acute coronary insufficiency. Of these 13 patients, 10 had a Grade 3 or 4 ballistocardiogram abnormality. From this the symptoms of acute myocardial infarction and acute coronary insufficiency are interpreted as representing a more severely damaged myocardium with greater impairment in contractile power. The reverse was true in the 13 remaining patients without histories of acute episodes. Only 3 of these patients had ballistocardiogram tracings above Grade 2, although all were abnormal.

Having demonstrated abnormal ballistocardiographic changes in all of a series of patients with typical angina pectoris with or without objective cardiac abnormalities, an atypical group of cases was studied in a similar manner, in which the diagnosis was suspected but not proved. Groups II, *A* and II, *B* include 24 such cases. Of these groups 21 patients showed varying degrees of abnormality of the ballistocardiogram, although only 11 of the 21 had one or more of the usual stigmas of cardiovascular abnormality. Three patients with no other objective evidence of cardiac abnormality and with normal ballistocardiograms were thought at the time to be suffering from anxiety states. The present evaluation of these cases

TABLE 1.—*Group I, A: Typical Cases of Angina Pectoris without Objective Evidence of Cardiac Abnormality*

Case No.	Patient	Age	Sex	Duration of Symptoms	Symptoms					Digitalis	Physical Findings			Laboratory Findings	
					Acute Coronary Insuff.	Myocardial Infarction	Angina Pectoris Typical	Angina Pectoris Atypical	History of Congestive Failure		Blood Pressure	Cardiac Enlargement	Heart Murmurs	Electrocardiogram	Classification of Ballistocardiogram
				years											*Grade*
1	A. F.	54	F	4½	0	0	+	0	0	0	137/70	0	0	0	1
2	M. W.	60	F	2	0	0	+	0	0	0	114/60	0	0	0	2
3	J. F.	55	M	1	0	0	+	0	0	0	130/80	0	0	0	2
4	W. D.	54	M	4½ months	0	0	+	0	0	0	140/80	0	0	0	1
5	M. O.	51	M	3 months	0	0	+	0	0	0	125/85	0	0	0	1

TABLE 2.—*Group I, B: Typical Cases of Angina Pectoris with Objective Evidence of Cardiac Abnormality*

Case No.	Patient	Age	Sex	Duration of Symptoms	Symptoms					Digitalis	Physical Findings			Laboratory Findings	
					Acute Coronary Insuff.	Myocardial Infarction	Angina Pectoris Typical	Atypical Case	History of Congestive Failure		Blood Pressure	Cardiac Enlargement	Heart Murmurs	Electrocardiogram	Classification of Ballistocardiogram
				years											*Grade*
1	J. F.	75	M	3	0	0	+	0	0	0	140/80	+	+	0	3
2	C. N.	56	M	5	0	0	+	0	0	0	100/60	0	0	+	1
3	A. S.	58	M	2 wks.	0	0	+	0	0	0	118/80	0	0	+	2
4	A. P.	64	M	5 months	0	0	+	0	0	0	130/80	0	+	+	1
5	O. B.	59	M	6	0	0	+	0	0	0	120/72	0	0	+	3
6	N. G.	51	M	5 months	0	0	+	0	0	0	130/90	0	+	+	2
7	T. S.	59	F	7 months	0	0	+	0	0	0	100/60	+	+	+	2
8	E. H.	49	M	4	0	0	+	0	+	+	130/70	+	+	+	4
9	F. S.	59	M	10	+	0	+	0	0	0	100/80	0	0	0	1
10	E. S.	65	M	14 months	+	0	+	0	0	0	160/90	0	0	0	3
11	J. M.	72	F	8	+	0	+	0	0	0	110/60	+	0	+	3
12	T. C.	70	M	13	+	0	+	0	+	+	160/80	0	+	+	2
13	R. B.	59	M	4 months	+	0	+	0	0	0	124/88	0	+	0	3
14	A. T.	31	M	9 months	+	0	+	0	0	0	120/80	0	+	+	3
15	L. C.	67	F	5	+	0	+	0	+	+	142/80	+	+	+	3
16	J. D.	66	M	2	+	0	+	0	0	0	130/80	+	0	+	3
17	F. R.	50	M	8	0	+	+	0	0	0	115/80	0	0	+	3
18	L. W.	53	M	6 wks.	0	+	+	0	0	0	92/60	0	0	+	4
19	L. F.	71	M	3	+	+	+	0	+	+	118/80	+	+	+	3
20	N. D.	48	M	3	+	+	+	0	+	+	100/70	+	+	+	2
21	L. C.	53	F	12 wks.	0	+	+	0	+	+	120/90	+	+	+	3

TABLE 3.—*Group II, A: The Atypical Case without Evidence of Cardiac Abnormality*

Case No.	Patient	Age	Sex	Duration of Symptoms	Symptoms					Digitalis	Physical Findings			Laboratory Findings	
					Acute Coronary Insuff.	Myocardial Infarction	Angina Pectoris Typical	Atypical Case	History of Congestive Failure		Blood Pressure	Cardiac Enlargement	Heart Murmurs	Electrocardiogram	Classification of Ballistocardiogram
				years											*Grade*
1	A. S.	53	F	3	0	0	0	+	0	0	140/90	0	0	0	2
2	M. P.	59	M	2 months	0	0	0	+	0	0	160/80	0	0	0	3
3	L. B.	54	M	6 months	0	0	0	+	0	0	116/70	0	0	0	3
4	H. G.	60	M	4 months	0	0	0	+	0	0	130/84	0	0	0	1
5	L. S.	38	F	4	0	0	0	+	0	0	154/84	0	0	0	0
6	R. B.	25	M	1	0	0	0	+	0	0	150/90	0	0	0	0
7	W. M.	44	M	4 months	0	0	0	+	0	0	120/80	0	0	0	1
8	G. P.	66	F	2½	0	0	0	+	0	0	125/80	0	0	0	3
9	J. K.	40	M	4 wks.	0	0	0	+	0	0	120/80	0	0	0	1
10	H. H.	57	M	6 months	0	0	0	+	0	0	120/80	0	0	0	2
11	F. D.	50	M	1 month	0	0	0	+	0	0	132/98	0	0	0	2
12	N. G.	41	M	3	0	0	0	+	0	0	120/85	0	0	0	2
13	H. G.	45	M	1	0	0	0	+	0	0	130/90	0	0	0	0

TABLE 4.—*Group II, B: The Atypical Case with Evidence of Cardiac Abnormality*

Case No.	Patient	Age	Sex	Duration of Symptoms	Symptoms					Digitalis	Physical Findings			Laboratory Findings	
					Acute Coronary Insuff.	Myocardial Infarction	Angina Pectoris Typical	Atypical Case	History of Congestive Failure		Blood Pressure	Cardiac Enlargement	Heart Murmurs	Electrocardiogram	Classification of Ballistocardiogram
				years											*Grade*
1	W. Z.	60	M	1	0	0	0	+	0	0	125/85	+	0	0	1
2	M. L.	51	F	1	0	0	0	+	0	+	130/85	+	0	0	2
3	C. S.	46	M	1½	0	0	0	+	0	0	130/90	0	+	0	2
4	H. E.	29	M	2	0	0	0	+	0	0	120/70	0	+	0	1
5	M. P.	52	F	2½	0	0	0	+	0	0	130/80	0	0	+	4
6	A. S.	42	F	2	+	0	0	+	+	+	110/70	0	0	+	3
7	E. S.	55	M	4	0	0	0	+	0	0	100/50	0	0	+	2
8	E. P.	56	M	5 months	0	0	0	+	0	0	140/90	0	0	+	1
9	J. L.	47	M	3 months	0	0	0	+	0	0	150/85	+	0	+	2
10	W. B.	66	M	2	0	0	0	+	0	0	154/64	+	+	+	3
11	C. M.	87	M	2	0	0	0	+	0	0	120/80	+	+	+	1

TABLE 5.—*Statistical Summary*

	Typical Cases of Angina Pectoris				Atypical Cases	
	I, *A*—Without Cardiac Abnormality	I, *B*—With Cardiac Abnormality			II, *A* Without Cardiac Abnormality	II, *B* With Cardiac Abnormality
		Entire Group	With Acute Coronary Insufficiency	With Acute Myocardial Infarction		
Number of cases	5	21	8	5	13	11
Men	3	17	6	4	10	8
Women	2	4	2	1	3	3
Cardiac enlargement	0	9	3	3	0	5
Heart murmurs	0	12	4	3	0	4
Positive E.C.G.	0	17	5	5	0	7
Positive B.C.G.	5	21	8	5	10	11
Grade 1	3	3	1	0	3	4
Grade 2	2	5	1	1	4	4
Grade 3	0	11	6	3	3	2
Grade 4	0	2	0	1	0	1

seems to substantiate that conclusion. It should be remembered that the patients in this group were those clinically suspected of having heart disease but in whom sufficient corroborative evidence was lacking. In view of the previous evidence the ballistocardiographic abnormalities in these two groups give support to the diagnosis of angina pectoris.

Finally, the duration of symptoms in the atypical cases was 17.3 months as compared to 39.2 months for the typical cases (excluding the 5 patients with acute myocardial infarction). This suggests that many patients with coronary artery disease may have atypical complaints preceding the development of classic and easily recognizable symptoms.

It is also an accepted belief that a considerable number of patients may present no signs or symptoms although there may be a moderate degree of arteriosclerosis of the coronaries.[15] The patient who ultimately suffers an acute myocardial infarction, "who never had a sick day or a pain in his life," is in this category. It is felt that between this group and the typical group are a great many patients with atypical complaints.

It must be emphasized that angina pectoris is no more than a symptom and its absence does not exclude the diagnosis of coronary artery disease. The common finding of abnormal ballistocardiograms in supposedly healthy patients over 50 years of age should not be surprising when the incidence of heart disease is recalled.[16] Since the other criteria may often be negative, there remains a large group of asymptomatic or atypical cases requiring curtailment of activity. It would seem from the empiric evidence presented that the ballistocardiogram will furnish objective evidence of circulatory abnormality in such cases by revealing defective mechanical heart action.

Conclusions

1. Studies of typical cases of angina pectoris established a definite relationship between this symptom complex and abnormal mechanical heart action as determined by the ballistocardiogram.

2. This relationship enables one to use the instrument as a diagnostic aid in the atypical cases of angina pectoris.

3. It is suggested that there is another group of individuals who, devoid of symptoms or known stigmas of cardiovascular abnormality but discovered to have mechanical impairment of the heart action, as determined by the ballistocardiogram, should be regarded as predisposed to angina pectoris or coronary thrombosis.

4. The physiologic significance of the movements imparted to the body by the heart beat, as revealed in the ballistocardiogram, must be sought if the symptoms of angina pectoris are to be understood fully.

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ABSTRACTS

BLOOD VESSELS AND VASCULAR DISEASE

Blain, A., III, and Campbell, K. N.: Lumbar Sympathectomy for Arteriosclerosis Obliterans. Surgery **25:** 950 (June), 1949.

The authors present their experience with sympathectomy in the treatment of arteriosclerosis obliterans. After a review of the literature and a study of their own cases, they arrive at the conclusion that this procedure reduces but rarely completely cures intermittent claudication. The pain associated with ulceration, however, is relieved even before the ulcer is healed. Small areas of superficial gangrene may actually disappear.

Contraindications to the use of sympathectomy are marked atrophy of the extremity with loss of subcutaneous tissues and consequent diminution in the available vascular bed, constant intractable pain uninfluenced by sympathetic block, the rapid onset of symptoms and a rapidly progressive vascular lesion.

It is the authors' opinion that sympathectomy appears to be a very effective procedure in the treatment of selected cases of arteriosclerosis of the lower extremities.

ABRAMSON

Friedell, M. T., Schaffner, F., Pickett, W. J., and Hummon, I. F., Jr.: Radioactivie Isotopes in the Study of Peripheral Vascular Disease. I. Derivation of a Circulatory Index. Arch. Int. Med. **83:** 608 (June), 1949.

Using radioactive phosphorus injected intravenously, the authors attempted to study the peripheral circulation in a series of normal subjects and in a group of patients with arteriosclerosis obliterans. By means of a scaling Geiger-Müller counter, with a probe type of tube which was applied to the sole of the foot, they were able to study the rate of deposition of the material in the tissues of the lower extremities. They found that for those patients with arteriosclerosis obliterans there was a greater build up than for normal individuals, indicating that the radioactive ion diffused into the tissues at a faster rate in the former. This was interpreted as indicating that in arteriosclerotic patients capillary dilatation is always present. From their studies, the authors derived a circulatory index which they believed had diagnostic and prognostic characteristics.

ABRAMSON

Schaffner, F., Friedell, M. T., Pickett, W. J., and Hummon, I. F., Jr.: Radioactive Isotopes in the Study of Peripheral Vascular Diseases. II. Method of Evaluation of Various Forms of Treatment. Arch. Int. Med. **83:** 620 (June), 1949.

The authors utilized their circulatory index, derived from the rate of deposition of radioactive phosphorus in the tissues of an extremity, to determine the therapeutic value of histidine monohydrochloride and ascorbic acid, lumbar sympathetic block with procaine, tetraethylammonium chloride, and lumbar sympathectomy. The patients were classified into four groups on the basis of the resulting change in their circulatory index. In one group the index was originally low and then rose toward normal. This type of response was interpreted as indicating a return of normal capillary tonus. In the second group the index was low initially and then fell, suggesting the capillary dilatation still persisted, although minor vasospastic elements were relieved. In the third group the index was first normal and then fell. This was interpreted to result from a persistence of capillary dilatation but a removal of major vasospastic elements. In the last group the circulatory index was originally above normal and then rose even higher. This occurred in patients with severe degree of impairment of circulation. The physiologic basis for this arbitrary classification is not included.

ABRAMSON

Moschcowitz, E.: The Association of Capillary Sclerosis with Arteriosclerosis and Phlebosclerosis; Its Pathogenesis and Clinical Significance. Ann. Int. Med. **30:** 1156 (June), 1949.

Capillary sclerosis is an invariable accompaniment of the general sclerotic process that affects the vascular system. When the main artery of an organ is affected by arteriosclerosis, the distal capillaries reveal capillary sclerosis. When the main vein of an organ is affected by phlebosclerosis, the proximal capillaries also show sclerosis. Evidence has been submitted to show that arterial and venous hypertension within these vessels is the cause of the

sclerotic process. In the pancreas and kidney, however, a decrescent capillary sclerosis, that is, sclerosis unassociated with hypertension, may occur; there is reason to believe that this is the result of prolonged normal intra-arterial tension, since it is associated with the decrescent arteriosclerosis of advanced years. A decrescent venocapillary sclerosis is probably impossible, since venous pressures are low and even under abnormal conditions never approach the normal systemic arterial pressures. Decrescent capillary sclerosis in the lung has not been observed for the same reason, since the pressure in the pulmonary artery is only one-sixth that within the aorta. Capillary sclerosis affects the function of organs to a greater or lesser extent. Teleologically, the early phases of capillary sclerosis represent a compensatory adaptation to the prolonged arterial and venous hypertension.

WENDKOS

Grayson, J.: Reactions of the Peripheral Circulation to External Heat. J. Physiol. **109:** 53 (July), 1949.

The effects of variations in environmental temperatures were studied in normal human subjects with the use of an improved plethysmograph for the measurement of finger and forearm blood flows.

As the environmental temperature rises to about 36 C., there is an increase in skin blood flow, with no change in muscle blood flow; the body temperature remains normal or falls slightly. When the external temperature rises to 40 C., there is a *decrease* in skin blood flow, again without change in muscle blood flow or significant change in body temperature. With the elevation of environmental temperature to over 40 C., there is an increase in skin blood flow. The body temperature now increases and perspiration begins. Vasodilation in both skin and muscles is found. The forearm blood flow does not change until the body temperature has risen.

Experiments on patients before and after sympathectomy indicate that the efferent pathway for all these effects is in the sympathetic nerves.

The vasoconstriction in the skin in response to temperatures higher than the body may be a regulating mechanism protecting the body against external heat.

WAIFE

Janes, J. M., and Musgrove, James E.: Effect of Arteriovenous Fistula on Growth of Bone: Preliminary Report. Proc. Staff Meet., Mayo Clin. **24:** 405 (Aug.), 1949.

Patients having congenital arteriovenous communications often have a long extremity on the effected side. Also, children who have had anterior poliomyelitis before closure of the epiphyses often have a short extremity on the side which has been severely involved in the disease. With these two facts in mind it occurred to the authors that by creating an arteriovenous fistula between the major vessels of one of the hind legs of a puppy they might be able to produce a long extremity. In each of 5 young dogs (less than 6 months old) an arteriovenous communication was made between the external iliac artery and vein of the left hind leg, and actual measurements of the femur and tibia were made three to fourteen months after the fistula was established. The right tibia and fibula were used as controls. From these studies it would appear that the length and circumference of the main bones of an extremity of a dog actually can be increased if a fistula was created before the epiphyses had closed.

SIMON

Greenblatt, I. J., Feldman, S., and Linder, J. M.: Use of Histamine in a Retarding Menstruum in Peripheral Vascular Disease. J. A. M. A. **141:** 260 (Sept. 24), 1949.

A group of 93 patients with peripheral vascular disorders were given daily injections of 1 to 2 cc. of histamine in a retarding menstruum, each cc. containing 0.5 mg. of histamine base, as the diphosphate, in 3 per cent yellow wax in sesame oil. Improvement was noted in 8 of 13 cases of thromboangiitis obliterans, in 14 of 30 cases of arteriosclerosis obliterans, and in 14 of 41 cases of diabetes and arteriosclerosis obliterans. In 22 patients determinations of the skin temperature of the toes revealed a higher and more prolonged elevation following histamine therapy than following paravertebral block.

HANNO

CORONARY ARTERIES AND CORONARY ARTERY DISEASE

Landman, M. E., Anhalt, H. S., and Angrist, A.: Asymptomatic Myocardial Infarction. Arch. Int. Med. **83:** 665 (June), 1949.

The authors studied 255 cases of myocardial infarction proved by gross and microscopic examination of necropsy material. Of these, 28 (or 11 per cent) were considered asymptomatic since they failed to show any evidences of pain, shock, dyspnea, or congestive failure. All infarcts in these cases were of considerable size so that necrotic muscle or a wide zone of scarred muscle was grossly obvious in all cases.

In differential diagnosis, the existence of asymptomatic infarcts becomes a consideration in any case of an obscure condition in a patient of the usual age group. Particularly in aged patients who fail to respond after operation, or who fail to respond to a treatment usually favorable for a certain condition, the presence of asymptomatic myocardial infarction must be suspected. Sudden cerebral insufficiency in aged people or sudden failure in any case, with or without shock, is often explained by such infarction. The authors stress the implication that functional alterations, not directly dependent on the existence

of necrotic muscle as such, may be the significant factor in determining the clinical syndrome during life, just as they are so often the fundamental basis for the understanding of the cause of death in cases of this syndrome.

BERNSTEIN

Sirkin, B., Bergman, H. C., and Prinzmetal, M.: Studies on Coronary Circulation V. Quantitative Changes in a Serum Mucoprotein Following the Occurrence of Myocardial Infarction. Am. J. Med. **6**: 734 (June), 1949.

In 23 patients with recent myocardial infarction, serum mucoprotein values were consistently found to exceed the normal range of 40 to 90 mg. per 100 ml. Serum levels were definitely elevated by the third day after clinical evidence of infarction and showed a peak value on the sixth day. This level was usually maintained for another week, then gradually declined to reach normal by the end of a month. Serum mucoprotein values were within the normal range in patients with chest pain due to angina pectoris, paroxysmal tachycardia, neurocirculatory asthenia, hypertension, and fibrositis. However, elevated serum mucoprotein values were noted in postoperative patients and in patients with cancer and pneumonia and a number of conditions characterized by a breakdown of tissue proteins.

No consistent relation was found between the sedimentation rate and serum mucoprotein. The sedimentation rates, however, generally remained elevated longer than serum mucoprotein following myocardial infarction. In vitro experiments on the relationship of the mucoprotein material to the sedimentation rate showed that serum mucoprotein had little or no influence on the acceleration of the sedimentation rate until concentrations were reached which were far beyond the usual elevated pathologic values found clinically after myocardial infarction.

Although serum mucoprotein elevation following myocardial infarction is not specific for this condition, the authors believe that it apparently reflects more accurately than the sedimentation rate or leukocyte count the presence or absence of myocardial necrosis.

SCHWARTZ

Simon, A. J., Dolgin, M., Solway, A. J. L., Hirschmann, J., and Katz, L. N.: A Re-evaluation of Papaverine in the Treatment of Angina Pectoris. J. Lab. & Clin. Med. **34**: 992 (July), 1949.

The authors studied the effect of Papaverine in 13 patients suffering from angina pectoris. After a six-week adjustment period, during which no medication was administered, and the patient's angina appeared to have reached a basic level, placebo (lactose) capsules identical in appearance with those containing Papaverine were given. After not less than four weeks on placebo therapy, capsules containing 100 mg. (1½ gr.) of Papaverine hydrochloride were substituted without the patient's knowledge, and after stabilization of response, the amounts were increased to 400, 600, and 800 mg. daily.

In only 2 patients was there a significant reduction in the number of attacks of pain on 400 mg. daily of Papaverine. One of these was unusually sedated by the drug. In no case was there a clear-cut improvement in ability to perform routine activities at any dosage level. No toxic symptoms were observed.

The authors state that Papaverine administered orally is of limited value in angina pectoris, although an occasional patient may show a striking beneficial effect without untoward side reactions.

BELLET

Dwyer, C. S., Kronenberg, S., and Saklad, M.: Anginal Syndrome during Sodium Succinate Therapy. Ann. Int. Med. 148 (July), 1949.

In a 65 year old woman, intravenous administration of sodium succinate appeared to bring about relief of intermittent claudication due to arteriosclerotic peripheral vascular disease, but it also precipitated attacks of angina pectoris. The mechanism for the apparently contradictory effects of the drug is not understood.

WENDKOS

Clawson, B. J., and Bell, E. T.: Incidence of Fatal Coronary Disease in Nondiabetic and in Diabetic Persons. Arch. Path. **48**: 105 (Aug.), 1949.

The authors reviewed the postmortem records at the University of Minnesota from 1910 through 1947 in order to determine the relative incidence of fatal coronary disease in nondiabetic and diabetic persons. Only those cases were included in which death was due primarily to coronary artery disease.

Beginning with the fourth decade, the percentage incidence of fatal coronary disease shows a heavy increase in the diabetic over that in the nondiabetic group; on the average, including all male patients from 40 years to 100, there is a two to one preponderance in the diabetics. In women, this preponderance is greater. Comparison of the nondiabetic and diabetic women in the age levels of 40 to 80 years shows a preponderance of fatal coronary disease of three to one. About 4 per cent of deaths due to coronary disease in man, and 14 per cent in women, are associated with diabetes.

GOULEY

Billings, F. T., Jr., Kalstone, B. M., Spencer, J. L., Ball, C. O. T., and Meneely, G. R.: Prognosis of Acute Myocardial Infarction. Am. J. Med. **7**: 356 (Sept.), 1949.

The authors analyze the important factors in the prognosis of 240 patients with myocardial infarction produced by acute coronary artery occlusion or severe acute coronary insufficiency. Ninety-seven of the patients died within thirty days of the acute

episode. In this group one or more of the following circumstances was a frequent finding: a prior history of congestive heart failure, delay in hospitalization, development of myocardial infarction during hospitalization for some other illness, evidence of congestive failure or circulatory collapse at the time of the attack, a pulse rate slower than 60 or faster than 110 beats per minute, a subnormal temperature or temperature above 101 F., cardiac enlargement, the presence of auricular fibrillation, and a leukocytosis in excess of 15,000.

In the group of 143 patients who survived the acute attack, follow-up information, which included data regarding the amount of physical activity engaged in by 120 of these patients, showed that the following factors adversely influenced the likelihood of a return to an active life: the occurrence of congestive heart failure before, during, or after the acute coronary episode, a history of rheumatic fever or peptic ulcer, the presence of advanced arteriosclerosis or diabetes mellitus, the occurrence during the attack of transient or persistent auricular fibrillation, gallop rhythm or extrasystoles, circulatory collapse and the presence of systolic murmurs.

SCHWARTZ

Adelsberg, D., Parets, A. D., and Boas, E. P.: Studies of Families with Xanthoma and Unselected Patients with Coronary Artery Disease under the Age of Fifty Years. J. A. M. A. **141:** 246 (Sept. 24), 1949.

Sixty-four patients with xanthomatosis and 137 members of the families of 35 of these patients were studied. Of these 201 persons, 49 (24 per cent) exhibited hypercholesterolemia, coronary artery disease, and one or more of the following: xanthoma tuberosum or tendinosum, xanthelasma, and corneal arcus. The serum cholesterol was elevated above 300 mg. per cent in 122 of the 175 cases tested. In 80 of the 201 subjects, coronary artery disease was present, and the serum cholesterol determined in 66 of these 80 patients was elevated above 300 mg. per cent in 57 cases. Cardiac symptoms developed before age 50 in 49 subjects.

For comparison, 122 patients under the age of 50 with coronary artery disease were investigated. Hypercholesterolemia was present in 71 (58 per cent), corneal arcus in 22, xanthelasma in 12, and xanthomatosis in 3. In addition, 50 familes of these 122 patients were studied. In fifteen families, all or most of the siblings exhibited hypercholesterolemia, as did one-half of the siblings in nine other families.

This study documents the close relationship in incidence among patients with hypercholesterolemia, coronary artery disease in relatively young subjects, and xanthomatous stigmata. From genetic analysis of the data, the authors conclude that the trait for hypercholesterolemia is inherited probably as an incomplete mendelian dominant; patients with xanthomatous manifestations are homozygous, whereas persons with uncomplicated coronary artery disease probably represent the heterozygous state.

HANNO

PULMONARY ARTERIES AND PULMONARY ARTERY DISEASE

Spitzbarth, H., and Fassbaender, H. G.: Complication of a Case of Solitary Aneurysm of the Right Pulmonary Artery by Pulmonary Tuberculosis. Ztschr. f. Kreislaufforsch. **38:** 78 (Feb.), 1949.

A 32 year old man with cyanosis presented a low pulse pressure (120/95), a systolic murmur was heard over the aortic area, a loud pulmonary second sound, right axis shift in the electrocardiogram and an x-ray pattern (enlarged left ventricle and prominent pulmonary arch) which suggested patent ductus arteriosus rather than aortic stenosis. The patient died of an acute dissemination of a tuberculous process in the right lung. Thrombotic occlusion of the main and right pulmonary artery and partial occlusion of the left at its ostium was found at post mortem. The primary thrombus was in an aneurysmal dilatation of the right pulmonary artery. A rheumatic etiology of this aneurysm seemed most probable. The impaired blood supply to the lungs suggested a causal connection between the aneurysm and the terminal exacerbation of the tuberculous process.

PICK

Delius, L., and Witzenhausen, R.: Pathogenesis and Consequences of Essential and Accidental Pulmonary Sclerosis. Ztschr. f. Kreislaufforsch. **38:** 87, (Feb.), 1949.

On the basis of the clinical and anatomic analysis of 2 cases, the authors stress the difficulties of the usual differentiation of primary and secondary sclerosis of the pulmonary vessels. They prefer a clinical and functional distinction of two types: (a) an "accidental" pulmonary hypertension with localized changes in the pulmonary circulation due to changes in some pulmonary vessels, and (b) an "essential" type either of unknown etiology or due to chronic inflammatory or embolic processes, leading to generalized sclerotic changes in the pulmonary vessels. The first type is without clinical importance. The second type runs a rapid and lethal clinical course.

PICK

Roh, C. E., Greene, D. G., Himmelstein, A., Humphreys, G. H., III, and Baldwin, E. DeF.: Cardiopulmonary Function Studies in a Patient with Ligation of the Left Pulmonary Artery. Am. J. Med. **6:** 795 (June), 1949.

The authors report the results of cardiopulmonary function studies performed on a patient two years after ligation of the left pulmonary artery. The results of pulmonary function tests were within normal limits, except for hyperventilation associated with a

decreased rate of oxygen removal at rest, during exercise, and in the post exercise recovery period. Cardiocirculatory studies showed normal pressures in the pulmonary artery and chambers of the right heart. The cardiac index was increased. However, bronchospirometry revealed that the left lung, although normally ventilated consumed a negligible amount of oxygen. The carbon dioxide output was diminished to a lesser degree than oxygen consumption, as determined by direct analyses of the expired air. The authors conclude that these findings are consistent with the assumption that anastomoses from the bronchial artery resulted in a considerable blood flow through the pulmonary capillary bed of the left lung.

SCHWARTZ

CEREBRAL ARTERIES AND CEREBRAL ARTERY DISEASE

Levine, Burton, Cheskin, Louis J., and Applebaum, Irving L.: Clinical Syndrome of Occlusion of the Posterior Inferior Cerebellar Artery. Arch. Int. Med. **84:** 431 (Sept.), 1949.

Three cases of the syndrome of occlusion of the posterior inferior cerebellar artery are presented. The onset is usually sudden and without loss of consciousness. The patient experiences dizziness and headache and falls toward the side where the lesion is located. There is associated nystagmus, difficult deglutition, homolateral Horner's syndrome, ataxia, trigeminal analgesia and thermanesthesia, and contralateral analgesia and thermanesthesia of the body.

Etiologically, arteriosclerosis is the most common factor but syphilis and metastatic neoplasm have all been involved. Prognosis with regard to life and the return of essential functions is generally good. The ataxia and inability to swallow often improve after several months. It must be remembered, however, that the syndrome is an indication of more generalized vascular disease, in which sudden death is not uncommon.

BERNSTEIN

HYPERTENSION

Peet, M. M., and Isberg, E. M.: Some Aspects of Hypertensive Disease of Pregnancy Treated by Splanchnicectomy. Am. J. M. Sc. **217:** 530 (May), 1949.

The results of 34 pregnancies in 28 hypertensive patients treated with bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy are reported. Of 18 cases who began pregnancy with normal blood pressures, 17 gave birth to 18 infants, and 15 were still maintaining normal blood pressure levels at a recent examination, averaging 2.7 years since delivery and 6.3 years since operation. On the other hand, of 10 cases who started pregnancies with blood pressure levels above 150/90, only 2 delivered living infants at term. Not one of the 18 cases who responded to splanchnicectomy by maintaining normal blood pressure levels after operation developed a toxemia of pregnancy. No splanchnicectomized patient suffered any late, harmful vascular effects as the result of pregnancy.

Five cases of toxemia superimposed upon prepregnant hypertension have been treated by splanchnicectomy performed during the second trimester of pregnancy, and in 2 cases the results have been excellent. Following operation, the toxemias disappeared and normal blood pressure levels were achieved for the remainder of the pregnancies and during a long postpartum follow-up period.

When female hypertensive subjects are divided into two groups, depending upon whether or not their hypertension had its origin during a pregnancy, there is little variance in their disease pictures, but there is significant difference in their overall response to splanchnicectomy. Both groups respond well to the operation, but the end-results are definitely better in the women whose hypertensive state began during a pregnancy.

The young hypertensive woman who wishes to have children should first have the essential hypertension treated by splanchnicectomy. If she maintains normal blood pressure levels for one year after operation, she may with reasonable safety become pregnant with the assurance that her chances are excellent for giving birth to a normal infant.

DURANT

Grimson, K. S., Orgain, E. S., Anderson, B., Broome, R. A., Jr., and Longino, F. H.: Results of Treatment of Patients with Hypertension by Total Thoracic and Partial to Total Lumbar Sympathectomy, Splanchnicectomy and Celiac Ganglionectomy. Ann. Surg. **129:** 850 (June), 1949.

The authors point out that there are a number of possible etiologic factors in hypertension which would not be affected by sympathetic denervation. However, theoretically at least, this type of procedure would be of value in neurogenic hypertension.

The results of operation on 113 hypertensive patients are presented. All subjects had a persistent elevation of systolic and diastolic blood pressure which did not decrease with medical treatment. Furthermore, all had suffered from some of the major complications of this disease, such as hemiplegia, hypertensive retinopathy with hemorrhages and exudates, definite decrease of renal function, and marked enlargement of the heart or abnormal electrocardiographic findings. The ages of the patients varied between 15 and 50 years, the average being 36 years.

Operations were accomplished in two stages. The stellate ganglion, all twelve thoracic ganglia, the first two lumbar ganglia, and the celiac ganglia were removed first on one side and three weeks later, on the opposite side.

Four of the 113 patients died in the hospital shortly after sympathectomy. Twelve died during the one to eight and one-half year period of post-

operative observation. The remaining 97 were still alive at the end of the period of study, the average survival time being 36.5 months.

Postural hypotension, with few exceptions, persisted during period of observation as long as eight and one-half years. Of the 97 patients who lived, 31 were considered as having reduction of blood pressure to near normal, 43 had reduction but not to normal, while 23 showed no significant decrease.

The symptoms referable to hypertension were definitely reduced or eliminated by sympathectomy. The eyeground findings were also markedly changed in the direction of normalcy. However, there were very few electrocardiographic alterations postoperatively.

The authors conclude that the extensive sympathectomy performed by them retards and in some instances arrests the progression of the hypertensive disease process. However, they emphasize the fact that this type of operation is associated with certain disabilities or inconveniences, such as pain, which may be intense, postural lowering of blood pressure, producing dizziness and other symptoms, excessive sweating in areas of regeneration or in areas not denervated, and obstruction of nasal airways caused by swelling of the mucous membranes.

ABRAMSON

Penick, R. M., Jr.: An Evaluation of the Treatment of Essential Hypertension by Sympathectomy. Ann. Surg. **129:** 872 (June), 1949.

On the basis of a study of 105 patients with hypertension treated with bilateral thoracolumbar sympathectomy and splanchnicectomy, the author attempts to determine whether the procedure is of value for the relief of symptoms and the prolongation of life. In each instance the sympathetic chain and splanchnics were removed from the level of the seventh thoracic vertebra down to the third lumbar ganglion.

The patients were re-examined at the end of one year following operation. It was the author's impression that sympathectomy caused relief of symptoms in more than 80 per cent of well-selected cases. However, he was unable to state definitely whether the procedure prolonged life.

ABRAMSON

Schroeder, H. A., Goldman, M. L., Futcher, P. H., and Hunter, M.: Low Sodium Diets in Hypertension: Effects on Blood Pressure. J. A. M. A. **140:** 449 (June 4), 1949.

Twenty-two hospitalized patients with essential hypertension were placed on diets containing from 0.5 to 2.0 Gm. of sodium chloride for periods of from ten to ninety days. In 13 patients, all of whom were in an advanced stage of hypertensive disease, no appreciable benefit was noted. A significant lowering of systolic and diastolic pressure levels resulted in 9 patients; 3 of this latter group were patients with relatively mild disease and 6 were obese women who manifested some of the findings characteristic of the Cushing syndrome. In the patients with an abortive or pseudo Cushing syndrome the levels of blood pressure appeared to be directly related to the sodium chloride intake, being lower when salt was restricted and higher when it was added. It is suggested that in such patients some dysfunction of the adrenal cortex exists.

HANNO

Evelyn, K. A., Alexander, F., and Cooper, S. R.: Effect of Sympathectomy on Blood Pressure in Hypertension: A Review of Thirteen Years' Experience at the Massachusetts General Hospital. J. A. M. A. **140:** 592 (June 18), 1949.

The authors review the five-year status of 100 essential hypertensive patients operated upon by the Smithwick procedure on the wards of the Massachusetts General Hospital. At the end of five years, 8 patients showed normal blood pressure levels, 13 showed significant reductions in blood pressure, 52 showed no significant blood pressure reduction, and 27 were dead. This constitutes a favorable five-year result in 21 cases and an unfavorable five-year result in 79 cases. A summary of the blood pressure status of the same 100 patients at the end of a two-year period revealed a favorable result in 41 cases and an unfavorable result in 59. These findings are taken to indicate that the results of sympathectomy tend to become less favorable as the length of the follow-up period increases.

HANNO

Alstad, K. S.: The Effects of Thiocyanate on Basal and Supplemental Blood Pressures. Brit. Heart J. **11:** 249 (July), 1949.

This report deals with the effect of potassium thiocyanate on the basal and supplemental blood pressures of 32 hypertensive patients. Control studies were made by replacing the drug with a placebo. Sixty-two per cent showed a fall in basal pressure of greater than 15/10 mm. of mercury. The greater reduction tended to occur in patients with lower and moderate basal pressures. No significant changes in basal pressure were obtained with a placebo. On the other hand, the supplemental pressure was reduced equally by the drug and by the placebo, which indicated that this reduction is a psychologic one. It is therefore concluded that thiocyanate therapy had two effects, one a direct one on the basal pressure and the other an indirect one, a psychologic effect, which together account for the reduction in the casual blood pressure.

SOLOFF

Keith, M. A., Woolf, B., and Gilchrist, A. R.: The Results of Medical and Surgical Treatment of Essential Hypertension. Brit. Heart J. **11:** 287 (July), 1949.

The authors treated 96 hypertensive patients medically over a five year period and 55 surgically over a nine year period. The medical and surgical patients were matched as closely as possible by grouping them together according to the severity of (1) symptoms (2) the diastolic pressure (3) renal function (4) cardiac function and (5) retinopathy. The authors conclude that the surgically treated patients with benign hypertension showed superior results in all five categories. There was however no statistical difference in mortality rate. In the group with malignant hypertension the data suggest that a greater well being and perhaps an increase in life span occur after surgery.

SOLOFF

Taliaferro, I., Adams, R. A., and Haag, H. B.: Benzodioxan Test: Fall in Blood Pressure Following Its Use in a Case of Renal Hypertension. J. A. M. A. **140:** 1271 (Aug. 20), 1949.

A case of renal hypertension is reported in which an initial intravenous administration of benzodioxan effected a sharp fall in the systolic and diastolic blood pressures. On two subsequent occasions, benzodioxan brought about progressively smaller falls in blood pressure, and a fourth administration of the drug resulted in no change in blood pressure.

Because of the marked depressor response to the first injection of benzodioxan, the possibility of pheochromocytoma was entertained. However, the intravenous administration of tetraethyl ammonium chloride produced a profound fall in blood pressure, and dibenamine intravenously and histamine intravenously resulted in no significant pressure changes. These findings are in contrast to the results reported following the administration of these agents in cases of pheochromocytoma; in such patients, histamine and tetraethyl ammonium bromide intravenously resulted in sharp blood pressure rises and dibenamine brought about a decrease in the pressure.

As a result of the findings in this case, the authors caution that a depressor response after benzodioxan does not necessarily indicate the presence of a pheochromocytoma.

HANNO

Ziskin, T.: Observations on the Hypophyseal Area in Hypertensions. Radiology **53:** 406 (Sept.), 1949.

The author studied 100 male patients with hypertension and a control group of 100 patients with normal blood pressure for the purpose of ascertaining if there was any relationship between the size of the pituitary, as determined by roentgen examination of the hypophyseal area, and hypertension.

The size of the pituitary fossa was determined by measuring the antero-posterior diameter and the depth. The lateral surface area was determined approximately by multiplying the two diameters. A slight but definite tendency to an increase in the size of the hypophyseal fossa in patients with hypertension was found. Comparison of the lateral surface areas when the cases are classified according to degree of systolic hypertension shows that the average size of the surface area tends to increase with the development of hypertension.

ZION

BACTERIAL ENDOCARDITIS

King, F. H., Schneierson, S. S., Sussman, M. L., Janowitz, H. D., and Stollerman, G. H.: Prolonged Moderate Dose Therapy Versus Intensive Short Term Therapy with Penicillin and Caronamide in Subacute Bacterial Endocarditis. J. Mt. Sinai Hosp. **16:** 35 (May–June), 1949.

The authors treated a series of 8 typical cases of subacute bacterial endocarditis by the method of massive short term therapy with penicillin and Caronamide to test the effectiveness of intensive treatment. In each case the treatment was completed within ten days or less. In spite of the successful maintenance of very high blood penicillin levels for ten days, the infection persisted in 7 out of 8 cases. Four out of the 7 failures were subsequently cured by prolonged treatment with moderate doses. At autopsy, however, culture of the vegetations revealed the same organism that was isolated from the blood during life.

The authors believe that there is a possibility that the high levels achieved during short term therapy were actually detrimental. The possibility exists that short term therapy does not allow for thorough penetration of the focus of infection. No evidence was found to indicate that failure with massive therapy could be attributed to high resistance of the infecting organism. Within the range of resistance encountered in this series there was no relation between the amenability of the infection to control and the degree of resistance of the organism.

BELLET

Luttgens, William F.: Endocarditis in "Main Line" Opium Addicts. Arch. Int. Med. **83:** 653 (June), 1949.

The author reports 13 cases of endocarditis following intravenous injections of opium by addicts who used no sterile precautions. The causative organism in 7 cases was a nonhemolytic streptococcus (possibly an enterococcus) resistant to penicillin. In 2 cases, *Streptococcus faecalis* was the invader. A species of Candida was present in one of the cases which also had a streptococcal infection. *Escherichia coli* was present in one case. *Aerobacter aerogenes* was found in one case (a cure was effected with streptomycin). *Pseudomonas aeruginosa* was present in one case and no organism was found in one instance.

The aortic valve was involved in 10 cases, the mitral valve in 2 cases, and the tricuspid valve in one case. No definite evidence of rheumatic, congenital, or syphilitic heart disease was present in any

of these cases, implying that normal valves can become infected after repeated injections of bacteria into the bloodstream.

BERNSTEIN

Wall, R., and Brundage, O.: The Treatment of Subacute Bacterial Endocarditis with Penicillin and Sodium Para-aminohippurate by Continuous Intravenous Drip. Ann. Int. Med. **30:** 1295 (June), 1949.

A case of subacute bacterial endocarditis due to *Streptococcus viridans* is presented. Two previous attempts at penicillin treatment were unsuccessful in arresting the disease process. The daily intravenous administration of a solution containing 5,000,000 units of penicillin for thirteen days, plus 200 Gm. of sodium para-aminohippurate for the last ten days of this treatment, is recorded as the treatment used. Heparin in small doses was added to facilitate the continuance of the constant venoclysis. Plasma penicillin levels showed a definite increase over the expected estimated levels. On the average they were greater with the administration of sodium para-aminohippurate concurrently. However, the authors feel this same elevation could be effected more easily by merely increasing the penicillin dosage. A follow-up of six months on this patient found him well and able to earn his living at his former occupation.

WENDKOS

Starrs, R. A.: Subacute Bacterial Endocarditis Presenting as a Subarachnoid Hemorrhage (Report of a Case with Recovery). Ann. Int. Med. 139 (July), 1949.

A case of subacute bacterial endocarditis is described, in which a subarachoid hemorrhage due to mycotic aneurysm constituted the first manifestation of the disease. Complete recovery occurred following the administration of large doses of penicillin. The organism responsible for the endocarditis was *Streptococcus viridans*. One year after discharge from the hospital, the patient had no complaint other than occasional slight fatigue and infrequent, mild palpitation. Examination at this time was negative except for the presence of systolic and diastolic murmurs at the cardiac apex.

WENDKOS

Lillian, M.: Multiple Pulmonary Artery Aneurysms. Am. J. Med. **7:** 280 (Aug.), 1949.

The author presents the case report with necropsy findings of a patient with widely patent ductus arteriosus and superimposed vegetative endarteritis, as well as saccular aneurysm of the pulmonary artery stem, mycotic aneurysms of the peripheral pulmonary arterial radicles, and congenital cyst formation in the lungs. Analysis of the case findings indicated that a vegetative endarteritis developed at the mouth of the ductus arteriosus following an attack of acute appendicitis with subsequent appendectomy. Following this there was dissemination of infected emboli resulting in aneurysm formation, pulmonary infarctions, and focal embolic glomerulonephritis. Rupture of an expanding hematoma caused by a mycotic aneurysm probably through one of the pulmonary cysts, caused a fatal hemothorax. The infectious process apparently had been controlled by massive penicillin therapy in the latter part of the patient's illness.

SCHWARTZ

Kaplan, S. R., Roseman, R. H., Katz, L. N., and Brams, W. A.: Healed Subacute Bacterial Endocarditis, A New Entity. J. A. M. A. **141:** 114 (Sept.), 1949.

Eighteen cases of subacute bacterial endocarditis cured by penicillin were followed for from twenty-five to sixty-one months. Progressive cardiac disability occurred in 6 patients, 3 succumbing to congestive heart failure; all 6 of these cases had dynamically significant aortic insufficiency. Twelve patients showed no evidence of progressive cardiac disability following cure of the bacterial infection; in none of these was dynamic aortic insufficiency present, although a diastolic aortic murmur was noted in 3 cases. No correlation could be found between progressive cardiac disability following cure of subacute bacterial endocarditis and age, sex, duration of illness prior to treatment, length of hospitalization, or total penicillin dosage.

From the findings in the cases reported by others and in their own 18 cases, the authors conclude that the presence of a dynamic aortic insufficiency following cure of subacute bacterial endocarditis presages progressive cardiac disability and bespeaks a poor outlook.

HANNO

Hudson, C. L., and Murray, J. B.: Eberthella Typhosa Infection of Arteriovenous Aneurysm Cured by Excision. J. A. M. A. **141:** 130 (Sept. 10), 1949.

A case is reported of *E. typhosa* infection of a pre-existing traumatic fistula between the axillary artery and vein in a patient recovering from typhoid fever. Surgical excision of the fistula effected a cure. The nature of the infecting organism makes this case unique.

HANNO

CONGENITAL ANOMALIES

Rodriguez Diaz, A., Castellanos, A., and Garcia, O.: Surprising Improvement in a Case of Pentalogy through Section of a Persistent Left Superior Cava. Arch. Inst. Cardiol. de Mexico **19:** 314 (March), 1949.

The first instance in which a persistent left superior vena cava was ligated is reported. The patient had a tetralogy of Fallot plus an interatrial septal

defect (the pentalogy of the Cuban school). The clinical conditions of the patient before the operation were very poor. After ligation and section of the vena cava, a remarkable improvement was observed.

LUISADA

Hansen, J. D. E.: Gangrene and Thrombosis in an Infant with Congenital Heart Disease. Arch. Dis. Child. **24:** 49 (June), 1949.

The author presents a case of gangrene of the left lower extremity in a male infant 10 weeks of age. He had been cyanotic from birth and was first seen at the age of 1 month when it was noted that he had an enlarged heart and a harsh systolic murmur over the whole precordium. The onset of gangrene coincided with a period when fluid intake had been low for several days, and it seems possible that thrombus formation at this time occluded the blood supply to the feet. The child became apathetic and prone to dyspneic attacks. Edema of the limbs spread to the trunk but there was no extension of the gangrene. Death took place on the thirteenth day after admission. Postmortem examination showed edema of the legs, sacrum, and back, with gangrene of both feet. The heart was enlarged, the right auricle being approximately twice the size of the left. There was transposition of the aorta and pulmonary artery. Thrombosis of the inferior vena-cava was present as high as the renal veins and extended into the gangrenous areas below the knees.

Thrombosis can be a complication of cyanotic congenital heart disease and it is particularly prone to occur when polycythemia becomes extreme, as in dehydration.

BELLET

Smith, K. S., and Wood, F. G.: Radiokymography in Patent Ductus Arteriosus. Brit. Heart J. **11:** 257 (July), 1949.

This report is an analysis of the findings of radiokymography on 16 patients who were subsequently operated upon for closure of a patent ductus arteriosus. Roentgen-kymographs were taken in the postero-anterior position.

Four special features were noted. The first two are regarded as direct effects of the patent ductus, the last two to associated hemodymanic effects produced by the patent ductus: (1) Para-aortic waves: These waves, present in 6 cases, were never seen in any other lesion and disappeared after ligation of the ductus. They are wave forms which lie parallel to and lateral to the aortic knuckle and are less dense than the aorta shadow. (2) Vibration waves: These waves were present in 12 cases and also disappeared after operation. They occurred below the aortic waves and blended with the pulmonary waves. They are regarded as the radiologic counterpart of the clinical thrill. (3) Exaggerated pulmonary artery waves: These waves were attributed to the prominent pulsatile pulmonary arc. (4) Exaggerated upper left ventricular waves: These waves were due to the vigorous contraction of the upper part of the left ventricle.

The authors concluded that radiokymography is valuable in helping to establish conclusively the diagnosis of a patent ductus arteriosus.

SOLOFF

Dotter, C. T., Hardisty, N. M., and Steinberg, I.: Anomalous Right Pulmonary Vein Entering the Inferior Vena Cava: Two Cases Diagnosed during Life by Angiocardiography and Cardiac Catheterization. Am. J. M. Sc. **218:** 31 (July), 1949.

Two instances of drainage of pulmonary veins from the entire right lung into the inferior vena cava have been presented in this report. These cases were diagnosed during life—an achievement not, to the reviewer's knowledge, previously reported.

Anomalous vascular channels causing drainage of pulmonary venous flow into the right heart or its tributaries have been reported in at least 133 cases. A total shunt is incompatible with prolonged life and is primarily of academic interest, both pathologically and embryologically. Partial emptying, however, is compatible with adult life (as in the 2 cases reported).

Both of the cases seem to bear out the hypothesis that a compensatory mechanism may effect a diminished function of the abnormally drained portion of lung. In one case there was definite diminished volume of the right (affected chest) as compared to the left, suggesting that respiratory volume was less on the affected side. In the other case the evidence was even more convincing. The left pulmonary artery was larger than normal and the left or "good" lung showed hypervascularity of the pulmonary arterial tree. In contrast, the right pulmonary artery as seen angiocardiographically was small in size and there was definite diminished vascularity of the pulmonary arterial ramifications. These changes are probably similar to functional disuse atrophy and hypertrophy in general. In effect these patients have what might be referred to as a functional congenital pneumonectomy. Surgical restoration of the normal anatomic relationships would appear to be a more difficult and drastic procedure than is warranted. Pneumonectomy would be indicated only in the presence or imminence of right heart failure.

As indicated by these cases the diagnosis may be made by angiocardiography and confirmed by cardiac catheterization. The findings by catheterization alone resemble those of interatrial septal defect and the differential diagnosis must depend on other evidence in most cases. In both of the cases presented, the clue to ultimate diagnosis was supplied by abnormal shadows of an apparently vascular nature seen in conventional roentgenograms. Angio-

cardiography is the most valuable means of diagnosis.

DURANT

Manhoff, L. J., and Howe, J. S.: Absence of the Pulmonary Artery: A New Classification for Pulmonary Arteries of Anomalous Origin. Arch. Path. **48:** 155 (Aug.), 1949.

The authors report a case of anomaly of the pulmonary artery, not classified in current nomenclature, namely, a complete absence of the pulmonary artery. They emphasize the difference between this anomaly and atresia of the artery, wherein the vessel may be represented by only a thin fibrous band. The difference is based on the nature of the underlying embryonic defect. In complete absence of the pulmonary artery and also of the ductus arteriosus, the primary cause is an absence of the primitive sixth aortic arch. The embryologic defects which lead to this anomaly and to the great hypertrophy of the bronchial arteries is discussed.

The authors record the case of a 10 month old child who died with lobar pneumonia; in the latter months of life a systolic murmur was heard over the precordium and there was progressive dyspnea.

At necropsy the heart showed no evidence of a pulmonary valve or a subvalvular stenosis and no pulmonary artery. The bronchial arteries were enormously hypertrophied and there was an associated dextraposition of the aorta and an interventricular septal defect.

In some cases no murmur has been detected, yet the other signs of the tetralogy of Fallot were notable. This anomaly does not result in as much cyanosis as is seen with the ordinary tetralogy, since the bronchial arteries develop to an unusual degree and permit adequate oxygenation in the lungs.

GOULEY

OTHER CARDIOVASCULAR DISEASES

Hartney, J. B., Biederman, A. A., Blumberg, J. M., and Leedham, C. L.: Primary Systemic Amyloid Disease; Report of a Case Emphasizing Cardiac Involvement. Arch. Path. **47:** 598 (June), 1949.

The authors report a case of primary systemic amyloidosis occurring in a 39 year old white woman who suffered a transient hemiplegia. In the last two years she had increasing dyspnea, paroxysmal nocturnal dyspnea, and leg edema. The heart was enlarged. The blood pressure was 105/75, while the venous pressure was increased, as was circulation time. The electrocardiogram showed low voltage in the limb leads with flattened or inverted T waves; the latter were inverted also in CF4, 5, and 6. The liver was large and hard, the spleen nonpalpable. Except for a hypoproteinemia with sharp reversal of the A-G ratio, liver function tests were normal. Sudden circulatory collapse accompanied by intensification of her hemiplegia was followed by death on the eighteenth hospital day.

Necropsy revealed a large heart weighing 600 grams. The left auricular endocardium was studded with semitranslucent plaques, shown later to be amyloid. The thick left ventricular wall did not show any unusual change grossly. Microscopically, however, the myocardium showed extensive amyloid infiltration varying from narrow ring deposits about individual fibers to large masses totally replacing the muscle. Both staining reactions were present. There was striking deposition in the wall of the small branches of the coronary arteries which occluded many of them. There was an extensive softening of the left cerebrum secondary to thrombosis of the anterior and middle cerebral arteries.

The authors record this case as one of "primary systemic amyloidosis" in spite of the extensive liver and splenic deposition characteristic of the "secondary" type of the disease usually associated with tuberculosis or chronic suppuration. They emphasize the commonly-noted cardiovascular involvement, with striking electrocardiographic changes. The diffuse myocardial infiltration by amyloid is the basis for such abnormal tracings.

GOULEY

Gore, Ira, and Arons, Walter: Calcification of the Myocardium. Arch. Path. **48:** 1 (July), 1949.

At the Army Institute of Pathology the authors collected 13 cases in which microscopic evidence indicated the presence of myocardial calcification. The common pathologic factor leading to calcification was necrosis of the myocardium, brought about by ischemia in 4 cases, by infectious myocarditis in 3 cases, and by a degeneration of unknown character in 4 cases. Advanced kidney disease was present in almost all cases. In 11 cases there was blood nitrogen retention. In the single case without renal insufficiency, myocardial calcification was caused by hypervitaminosis D.

GOULEY

Boucek, Robert J., Bailey, Allan A., Burchell, Howard B., and Edwards, Jesse E.: Cardiac Clinics. CXXX. Myocardial Disease in Acute Poliomyelitis. Proc. Staff Meet., Mayo Clin. **24:** 495 (Sept.), 1949.

The occurrence of myocardial changes in certain cases of poliomyelitis are being more widely recognized. These lesions are not specific for poliomyelitis; however, they do resemble closely the lesions produced by other viral diseases and they may influence the course of the underlying disease.

The case of a man, 29 years of age, who had spinal and bulbar poliomyelitis and associated myocardial disease is reported. Clinically, a picture of pulmonary edema and peripheral circulatory failure was present preceding the fatal outcome. A single electrocardiogram revealed slightly elevated S-T segments and diphasic T waves in Lead I. It seemed possible that these changes could be related to the concentration

of myocardial lesions in the antero-lateral wall of the left ventricle, which were demonstrated pathologically. These changes consisted of myocarditis with cellular infiltration, necrotizing changes in muscle fibers and generalized edema of the cardiac muscle. Whether the pulmonary edema and circulatory collapse were caused by the medullary involvement alone, by the myocardial changes alone, or by a combination of these two factors was impossible to determine.

SIMON

CONGESTIVE HEART FAILURE

Bryant, J. M., Iob, V., Phillips, G. L., and Blecha, E. E.: Estimation of Urinary Sodium: A Simple Test for Patients on Low Sodium Diets J. A. M. A. **140:** 670 (June 25), 1949.

As an aid in the control of patients on low sodium diets, a simplified test for the estimation of the daily urinary excretion of sodium is presented. The value of the test, which can readily be performed by the patient on a morning sample of urine, is comparable to that of the simplified Benedict reaction in the management of diabetes. The test is a determination of the chloride concentration by means of standardized solutions of silver nitrate and potassium chromate; from the chloride concentration the concentration of sodium may be estimated. The ingestion of halides other than sodium chloride results in erroneously high sodium estimations, and urinary sodium resulting from the ingestion of sodium compounds other than the chloride cannot be detected.

HANNO

Schneierson, S. J.: Continuous Peritoneal Irrigation in the Treatment of Intractable Edema of Cardiac Origin. Am. J. M. Sc. **218:** 76 (July), 1949.

Continuous peritoneal irrigation with 5 per cent glucose was used in a case of rheumatic heart disease with mitral stenosis, auricular fibrillation, and congestive heart failure with massive edema in whom conventional measures proved futile. A No. 24 mushroom catheter and a Sump drain were used according to the method of Seligman, Frank, and Fine. This procedure was followed by great loss of edema fluid and "short term" striking improvement of the patient. The drainage fluid from the peritoneal cavity contained significant concentrations of sodium.

DURANT

Batterman, R. C., Unterman, D., and DeGraff, A. C.: The Subcutaneous Administration of Mercaptomerin (Thiomerin): Effective Mercurial Diuretic for the Treatment of Congestive Heart Failure. J. A. M. A. **140:** 1268 (Aug. 20), 1949.

The clinical evaluation of a new mercurial diuretic, mercaptomerin sodium (Thiomerin sodium), is presented. This drug is the disodium salt of N(gamma-carboxymethyl - mercaptomercuri - beta - methoxy) propyl camphoramic acid. Pharmacologically it has been demonstrated that this substance possesses less than one-one hundred and sixtieth the cardiac toxicity of the least toxic of the presently available mercurial diuretic preparations. Clinically, mercaptomerin administered subcutaneously evokes little or no local irritation and the degree of diuresis is similar to that obtained with the intravenous use of mercurophylline injection (Mercuhydrin). Mercaptomerin sodium administered subcutaneously is superior to other mercurial diuretics administered intramuscularly. Only 2 patients in the large group receiving mercaptomerin manifested any untoward effect; the reactions, characterized by mild chill and fever, were similar to the reactions exhibited by the same patients to previous injections of mercurophylline. The authors conclude that mercaptomerin is the mercurial diuretic of choice because it is safe, effective, and can be administered subcutaneously.

HANNO

ARRHYTHMIAS

Ferrer, M. I., Harvey, R. M., Weiner, H. M., Cathcart, R. T., and Cournand, A.: Hemodynamic Studies in Two Cases of Wolff-Parkinson-White Syndrome with Paroxysmal A-V Nodal Tachycardia. Am. J. Med. **6:** 725 (June), 1949.

Cardiac output, peripheral resistance, and stroke volume as well as intracardiac, peripheral arterial and peripheral venous pressure tracings were obtained in 2 patients with Wolff-Parkinson-White syndrome during the anomalous atrioventricular conduction, and also during an attack of supraventricular tachycardia in each of the 2 subjects. Information obtained in these studies suggested that in each patient the anomalous conduction pathway was located on different sides of the heart, and that ventricular excitation was abnormal in both ventricles during aberrant conduction.

In one case, a direct intracardiac lead permitted the electrocardiographic registration of intracavity potentials simultaneously with the intracardiac pressure curves. Identification of the supraventricular tachycardia as nodal could be made only by the intracardiac lead. There were marked pressure and presumably filling abnormalities in the right auricle related to tricuspid insufficiency and to the deranged time of auricular systole during the nodal tachycardia. The cardiac output was unchanged by these alterations despite the increased rate.

Intracardiac and arterial blood pressures and systemic flow were normal in one patient with anomalous A-V conduction and sinus rhythm. In the other patient the authors believe that abnormalities in these values could be ascribed to a coincident early cor pulmonale.

SCHWARTZ

Burchell, H. B.: Sino-auricular Block, Interference of Dissociation, and Different Recovery Rates of

Excitation in the Bundle Branches. Brit. Heart J. **11**: 230 (July), 1949.

The author analyzes in detail the electrocardiographic records obtained from a woman, age 60, which exhibited recurring phenomena of nodal rhythm with interference dissociation. The ventricular beat conducted from the auricle showed the presence of either left or right bundle branch block, depending upon the time relationship between the P wave that was to be followed by a ventricular response and the preceding R wave of the nodal beat. He concludes that different recovery rates in excitation of the two bundle branches can explain these phenomena without invoking the possibility of an intraventricular supernormal phase of recovery.

SOLOFF

RELATION OF ENDOCRINES TO CIRCULATION

Osterwald, K. H.: On the Effect of the Adrenal Cortical Hormones on the Circulation. Arch. f. Kreislaufforsch. **14**: 205 (Apr.), 1948.

On 9 dogs and 9 cats under Pernocton anesthesia, the thermostromuhr was applied to the inferior vena cava, the left pulmonary artery, the splanchnic, and the coronary arteries. From the results obtained, cardiac output and peripheral blood flow were estimated. Simultaneously systemic blood pressure and the pressure in the right auricle were taken.

The author found that adrenal cortical hormones (cortin, pancortex and desocycorticosterone) influenced the peripheral circulation in a way similar to epinephrine in physiologic dosage. If the animals were in a state of collapse following trauma, the blood pressure was increased and the cardiac output rose with the administration of the adrenocortical hormones. The increased cardiac output resulted from an increased venous return of blood to the heart. If the circulation was normal the cardiac output was not changed and only an alteration of the distribution of the blood was found.

The coronary blood flow increased parallel with the increased work of the heart caused by the rise of systemic blood pressure. No definite pattern of response of the splanchnic system could be detected.

SCHERF

Pinniger, J. L., and Brown, J. B.: Adrenal Pheochromocytoma. Arch. Path. **47**: 557 (June), 1949.

The authors report an unusual case of pheochromocytoma in a 58 year old woman, who developed evidence of left heart failure during her last year of life. The cause of failure remained obscure inasmuch as the blood pressure was normal, the heart was of normal size, and no murmurs were present. No subcutaneous edema was noted, but on the day of her death the patient's dyspnea was complicated by pulmonary congestive failure which was the immediate cause of death. Except for evidences of heart failure the only finding on physical examination was a nontender tumor in the left hypochondrium.

Postmortem examination revealed a spheroid tumor weighing 1,200 grams in the left abdomen. It lay above the kidney, which was pushed down into the pelvis. Section revealed a purplish fleshy mass in which normal adrenal cortex could not be found. The heart weighed 340 grams; the left anterior descending coronary artery was patent but narrowed by calcific atherosclerosis. The lungs were congested. The right adrenal gland was normal.

Microscopic examination showed that many portions of the tumor strongly resembled adrenal medulla. Chemical analysis revealed that the tumor contained 2.7 mg. of epinephrine per gram or a total of 3.2 grams, which with one exception is the largest amount recorded.

This case is unusual, in that the demonstration of a large tumor containing a high concentration of epinephrine is in sharp contrast with the clinical findings of a normal blood pressure, a normal-sized heart, and freedom from symptoms until one year before death. The tumor was probably many years in developing.

GOULEY

Kern, R. A., Soloff, L. A., Snape, W. J., and Bello, C. T.: Pericardial Effusion: a Constant, Early and Major Factor in the Cardiac Syndrome of Hypothyroidism (Myxedema Heart). Am. J. M. Sc. **217**: 609 (June), 1949.

"Myxedema heart" is of not uncommon occurrence in untreated myxedema and has heretofore been explained on the basis of a uniform dilatation of all the cardiac chambers. Little consideration has been given to pericardial effusion, a condition reported to date in only 21 cases of myxedema. Yet in 4 consecutive patients with this disease the authors have demonstrated considerable pericardial effusion, even when roentgenologic findings were not suggestive of its presence, and when any evidence of congestive failure was absent. In all 4 patients the effusion cleared up under thyroid medication, and in one patient this phenomenon was observed in two additional periods of hypothyroidism induced, with the patient's consent, by omitting treatment.

The electrocardiographic picture hitherto ascribed to myocardial changes and to the effects of tissue edema can even better be explained by the effect of a blanketing pericardial effusion. This view is not only suggested by the previous experimental evidence of others, but is strongly supported by the authors' findings of marked improvement between two tracings taken on the same day just before and just after the aspiration of the pericardial effusion.

The authors believe, therefore, that pericardial effusion is a constant, an early, and a major factor in the cardiac findings in myxedema, and that "myxedema heart" is not a cardiac disease, but a manifestation of the disease myxedema, and has the

much more favorable therapeutic and prognostic outlook of the latter.

DURANT

Holton, P.: Noradrenaline in Tumours of the Adrenal Medulla. J. Physiol. **108:** 525 (June), 1949.

Large amounts of noradrenaline were found in three pheochromocytomata. Tumor extracts were assayed against *l*-adrenaline and *d,l*-noradrenaline on rabbit's duodenum and rat's uterus. The concentration of noradrenaline activity ranged from 6 to 11 mg. per gram of tumor tissue.

WAIFE

Hildes, J. A., Purser, S. H., and Sherlock, S.: The Effects of Intra-arterial Adrenaline on Carbohydrate Metabolism in Man. J. Physiol. **109:** 232 (July), 1949.

Following the infusion of adrenaline into the femoral arteries of 10 normal men, no change was noted in the blood pressure, pulse rate, blood sugar, lactic acid, and serum potassium or in the glycogen content of the gastrocmenius muscle of the perfused limb.

Adrenaline has no direct glycogenolytic effect on muscle and is rapidly destroyed or inactivated and so produces no general effects on carbohydrate metabolism.

WAIFE

Grimson, K. S., Longino, F. H., Kernodle, C. E., and O'Rear, H. B.: Treatment of a Patient with a Pheochromocytoma: Use of an Adrenolytic Drug before and during Operation. J. A. M. A. **140:** 1273 (Aug. 20), 1949.

The surgical removal of pheochromocytomas is fraught with the danger of epinephrine intoxication as a result of the anesthetic agents and operative manipulation of the tumor. In an attempt to minimize this hazard, the authors utilized an adrenolytic drug, 2(N,para-tolyl-N (m-hydroxyphenol)-aminomethyl)-imidazoline hydrochloride, administered intravenously before and during surgery, in a boy with a benign pheochromocytoma. They found the drug useful in preventing extreme fluctuations of blood pressure during anesthesia and operative removal of the tumor.

HANNO

THROMBOEMBOLIC PHENOMENA

Wigginton, R. C., Parson, W. H., and Purks, W. K.: Thrombosis and Embolism. Ann. Surg. **129:** 784 (June), 1949.

On the basis of a series of 40 cases of venous thrombosis, with or without embolic phenomena, the authors attempt to evaluate the various factors responsible for the condition and the means for combating it.

The routine methods of prophylaxis were utilized. Embolism was present more often in the patients who were 60 years of age or over than in those in younger age groups. In 70 per cent of the series (28 patients), venous thrombosis occurred after pelvic operations. In 11 of the 17 cases of pulmonary embolism in the group, there was no evidence of a preceding thrombosis or thrombophlebitis, suggesting that in all these cases the emboli arose from silent, deep-seated phlebothrombosis. Uncomplicated thrombophlebitis became evident between the fourteenth and twenty-second days after operation and phlebothrombosis, between the fourth and fourteenth days. Dicumarol was administered in 26 of the 30 cases in which there was sufficient time to institute therapy. In addition, heat, elevation of the affected extremity and chemotherapy were utilized.

It is the author's impression that the wisest course is to institute dicumarol therapy on or about the fifth postoperative day in patients who present factors likely to produce vascular complications, regardless of the smoothness of the convalescence. However, the possibility must be considered that mass prophylaxis might introduce more problems than it would solve.

ABRAMSON

Pratt, G. H.: An Early Sign of Femoral Thrombosis. J. A. M. A. **140:** 476 (June 4), 1949.

Pratt has observed that compensatory dilatation of the pretibial veins is an early sign of thrombosis of the deep veins of the leg. This diagnostic sign was found to be present in 84 of 109 cases of venous thrombosis and occurred earlier in the course of the disease than edema or a positive Homan's sign.

HANNO

Madden, J. L.: Resection of the Left Auricular Appendix: A Prophylaxis for Recurrent Arterial Emboli. J. A. M. A. **140:** 769 (July 2), 1949.

In patients with rheumatic mitral stenosis, emboli resulting from cardiac mural thrombi are common. About 90 per cent of the mural thrombi in rheumatic hearts with mitral stenosis are located in the auricles, mainly in the left auricle and its appendix. In older age groups, in the presence of auricular fibrillation and in the presence of congestive failure, the incidence of mural thrombi rises.

In an effort to prevent further emboli, in 2 patients with rheumatic mitral stenosis and auricular fibrillation who had suffered recent peripheral arterial embolic occlusions, the author performed resection of the left auricular appendix. One patient died suddenly on the ninth postoperative day. In the case of the patient who survived the surgery, the operation was complicated by temporary cardiac standstill; postoperatively a hemiplegia and personality change were apparent.

The author states that resection of the left auricular appendix as a prophylaxis for recurrent arterial emboli is indicated in patients with rheumatic heart

disease and mitral stenosis, with or without auricular fibrillation, who have had one or more recent peripheral arterial embolic occlusions.

HANNO

BLOOD COAGULATION AND ANTICOAGULANTS

James, D. F., Bennett, I. L., Jr., Scheinberg, P., and Butler J. J.: Clinical Studies on Dicumarol Hypoprothrombinemia and Vitamin K Preparations. I. Superiority of Vitamin K_1 Oxide over Menadione Sodium Bisulfite U.S.P. and Synkavite in Reversing Dicumarol Hypoprothrombinemia. Arch. Int. Med. **83:** 632 (June), 1949.

The effect of Menadione sodium bisulphite, Synkavite, and vitamin K_1 oxide on the dicumarol effect was estimated on the basis of two factors: The time elapsing between the administration of the drug and the conversion of pronounced to moderate hypoprothrombinemia (from below 10 per cent of normal plasma to levels above this); and the time elapsing after administration of the agent until the appearance of a prothrombin level consistent with intravascular clotting. Vitamin K_1 oxide was more effective on both counts. Twenty-six patients given 0.5 Gm. intravenously had their prothrombin time arrive and stay at a level lower than that of 30 per cent normal plasma in an average of thirteen hours. It took 4.7 days with Menadione sodium bisulphite (64 to 180 mg. intravenously) and 5.3 days with Synkavite (100 to 500 mg. intravenously) to achieve similar results. It required only four hours for 0.1 Gm. or more of vitamin K_1 oxide to bring dangerous hypoprothrombinemic levels back to a safe range. The authors also found that 1 of every 5 patients required five or more days to achieve significant therapeutic effect from dicumarol in the usual doses. Individual subjects will respond in a predictable fashion to subsequent doses of dicumarol except after vitamin K_1 oxide which renders patients insensitive to dicumarol.

The need for several controls for proper prothrombin dilution curves is emphasized. The authors further show the variability of prothrombin times of plasma diluted to 10 per cent concentration with saline solution. This is felt to be due to a fibrinogen deficiency which the authors are trying to overcome by the use of prothrombin-free plasma as a diluent as suggested by other authors.

BERNSTEIN

Fowler, N. O.: A Study of Certain Aspects of Blood Coagulation in the Postoperative State in Congestive Heart Failure and in Thrombophlebitis. J. Clin. Investigation. **28:** 671 (July), 1949.

The coagulation of the blood may be studied by a variety of tests: the silicone tube, the lusteroid tube coagulation tests, clot retraction, Lee-White clotting test, the heparin retarded coagulation test of Waugh and Ruddick, the heparin tolerance test, and the prothrombin time. These tests were performed on 29 postoperative patients, 27 with congestive heart failure and 3 with acute thrombophlebitis.

The correlation among the tests was poor, suggesting that they are concerned with different factors in the clotting process. Of the various tests, the Waugh-Ruddick heparin test seemed the most sensitive. By this method, 19 of 29 postoperative patients showed accelerated coagulation. Hypercoagulability may persist for as long as twelve days postoperatively. However, the tests are of no value in predicting or diagnosing thrombophlebitis. Among the 27 patients with congestive heart failure, 25 of whom were receiving digitalis, only one showed accelerated coagulation in lusteroid tubes and 2 by the Lee-White test. The clotting time may be longer in a blood sample taken from a vein which had recently received heparin than from the opposite arm.

WAIFE

Margulies, H., and Barker, N. W.: The Coagulation Time of Blood in Silicone Tubes in Patients Receiving Dicumarol. Am. J. M. Sc. **218:** 52 (July), 1949.

Thirteen patients receiving dicumarol were studied. It was found that the changes in prothrombin time in these patients were associated with corresponding changes in the coagulation time in silicone tubes. Glass tubes used to measure coagulation time in the conventional way did not show these changes. The change in silicone-tube coagulation times was often not simultaneous with the change in the prothrombin time. Possible reasons for the lag are discussed. The relationship between prothrombin time and silicone coagulation time varied from one individual to another. The same prothrombin time in several subjects was accompanied by widely different coagulation times, so that it was not possible to correlate directly the prothrombin time of the patients studied with the silicone coagulation time that they manifested. Change in prothrombin time was, however, accompanied by alteration in coagulation time (in silicone tubes) which was consistently predictable in direction if not in magnitude.

DURANT

Jaques, L. B., Monkhouse, F. C., and Stewart, Mary: A Method for the Determination of Heparin in Blood. J. Physiol. **109:** 41 (July), 1949.

Heparin may be precipatated from citrated plasma by N-octylamine and reprecipitated with brucine. Recovery of 80–90 per cent of heparin added to whole blood of dogs was obtained, while heparin was completely recovered when added to plasma. This suggests either absorption of heparin by cells or incomplete removal of plasma. The proportion recovered was somewhat less in human blood.

Normal human blood contains about 0.0001 mg./ml. of "heparin" expressed as the free acid form. Following the injection of heparin into dogs high levels were reached, but these fell rapidly within an hour. The concentration then leveled off and gradually disappeared. The clotting time became measurable three hours after injection and rapidly returned to normal with the further decrease in blood heparin concentration.

WAIFE

ELECTROCARDIOGRAPHY

Rabina, P.: Early Electrocardiographic Diagnosis of Left Ventricular Hypertrophy. Arch. Inst. Cardiol. de Mexico **19:** 373 (March), 1949.

Two new signs for the diagnosis of early or well established left ventricular hypertrophy are reported. These signs are present sometimes even before the appearance of the radiologic evidences. The first sign is an S-T segment of horizontal or rectilinear appearance in which the beginning of the T wave is clearly discernible. The second sign consists of the presence of a high voltage of the R wave coincident with a low voltage of the T wave in Leads I, II, V_4, and V_5, and V_6.

LUISADA

Fox, T. T.: On the Significance of the Normal Electrocardiogram in Old Age. Ann. Int. Med. 120 (July), 1949.

One hundred inmates of an institution for the aged, who showed normal electrocardiograms, were followed for a period of seven years. By the end of the second year, 22 cases were found to have abnormal electrocardiographic tracings. By the end of the fourth year, 36 cases possessed abnormalities in the electrocardiogram. By the end of seven years, 47 inmates had abnormal changes in the electrocardiogram. S-T segment depression and T-wave inversion constituted the most frequent abnormality in this group. The other abnormalities consisted of bundle branch block, Q_2 and Q_3 changes, low voltage of QRS in the standard limb leads, nodal rhythm, first degree A-V heart block, auricular fibrillation, and auricular flutter. In evaluating the significance of the abnormal tracing, the related factors considered were age, the level of blood pressure, and the presence of cardiac enlargement. It became apparent that while the occurrence of the abnormal electrocardiogram in senescence has some prognostic significance, it is the presence of heart enlargement that is a better determining factor of the life span of the aged individual.

WENDKOS

Schlesinger, B., and Landtman, B.: Electrocardiographic Studies in Cretins. Brit. Heart J. **11:** 237 (July), 1949.

The authors studied 24 children with hypothyroidism to determine whether the electrocardiogram was of diagnostic significance. Electrocardiographic studies were begun in 10 children before any thyroid substance had been administered; the other 14 already had received some medication. The electrocardiograms were abnormal in all of the 10 untreated children and in 4 of the 14 who received insufficient thyroid medication.

No bradycardia was observed in the untreated subjects. The heart rate averaged 107 a minute and increased to 121 after treatment. Sinus arrhythmia was diminished in the untreated cretins. The voltage was decreased before treatment. Left axis deviation appeared in 5 cases after treatment. The P-Q interval decreased slightly after treatment. The duration of systole was prolonged in 7 and returned to normal limits after treatment. Changes in the R-T segment noted in 8 children were characterized by a sloping take off of the segment from the descending part of the initial complex or by convexity of the segment. Some three weeks of treatment were usually required for the disappearance of electrocardiographic changes.

The authors conclude that the electrocardiogram is of value (1) in establishing a diagnosis of hypothyroidism when the clinical evidence is inconclusive and (2) in regulating the dosage of thyroid substance.

SOLOFF

Meyer, P.: The Electrocardiogram of Posterior Cardiac Infarction. Brit. Heart J. **11:** 271 (July), 1949.

The electrocardiograms of 40 patients with posterior myocardial infarction were analyzed to determine the form of the QRS complex that remained in the healed stage. Seven had changes indistinguishable from normal variants. In electrically vertical hearts, Q_2 and Q_3 were of uncertain significance if Q_3 was less than 0.04 second in duration and if less than 25 per cent of the tallest R wave in any lead. In electrically transverse hearts, Q_3 was equivocal if small or absent in Lead II.

Unipolar extremity leads were taken in 18 cases. The left leg lead showed a deep, wide Q wave when Q_2 and Q_3 were characteristic. The Q wave was deeper in Lead III than in the left leg lead. In those instances with equivocal Q waves in the standard leads, equivocal findings were present in the left leg lead. In electrically vertical hearts, an inconclusive Q wave, usually of the same size as Q_3, was present in the left leg lead. In electrically horizontal hearts, the Q in the left leg lead was less wide than that usually associated with infarction and smaller than the Q wave of Lead III.

All cases of posterior infarction had an initial upward deflection in the left arm lead greater than one mm. and often broad and slurred. In 15 of the 18 cases, the initial deflection of the right arm was also upright and varied in amplitude from a small spike to a size of 4 mm. An R wave in the right

arm would be expected to show as a Q wave in Lead I, but in all 15 cases Q_1 was either absent or smaller than R in the right arm lead after allowance was made for augmentation.

The author suggests that the characterstics of the initial upward deflections of the left and right arm leads may aid in determining the significance of equivocal Q waves in the standard and left leg leads.

SOLOFF

Hunzicker, W. J., and Levine, H. D.: Clinical Evaluation of Direct Writing Electrocardiography. Am. J. M. Sc. **218:** 37 (July), 1949.

A direct writing electrocardiograph operating on the vacuum tube principle was capable of immediately recording tracings faithfully, duplicating those obtained with an acceptable camera type vacuum tube (amplifier) electrocardiograph. The occasional differences between tracings obtained with a direct writing and a string galvanometer type electrocardiograph were slight and clinically unimportant and in no case altered the interpretation made.

DURANT

Kuskin, L., and Brockman, L.: The Direction of the Precordial T Wave in 321 Normal Infants and Children. Am. J. M. Sc. **218:** 65 (July), 1949.

The direction of the T wave of five precordial leads was studied in 321 normal infants and children.

The T wave in CF_1 was inverted in 100 per cent of 129 children up to 6 years of age, except for one diphasic wave in a child 5 years of age. In the 12 to 14 year age group 78 per cent of the children had inverted T waves in this lead. In CF_2 the T wave was inverted in 90 per cent of children up to 4 years of age. In CF_3 the T wave followed the same pattern as in CF_2. The T wave in CF_4 was inverted in only 27 of the 321 children (8.3 per cent); in 20 it was diphasic. There was no inversion in 50 children aged 12 through 14 years. The T wave in CF_5 was inverted in 6 per cent of children up to 2 years of age, with no inversions in older children.

It is suggested that leads CF_2 and CF_3 offer no significant information that is not contained in CF_1, CF_4, and CF_5.

DURANT

ROENTGENOLOGY

Routier, D., Heim De Balsac, R., and Alessandris: Systolic Expansion of the Left Auricle as Roentgenologic Evidence of Mitral Insufficiency. Rev. argent de cardiol. **16:** 137 (May–June), 1949.

Fluoroscopic and roentgenkymographic methods were used for a study of the systolic expansion of the left auricle in 190 patients with mitral valvular disease. Left auricular systolic expansion is more frequent and of greater degree in cases with auricular fibrillation or increased volume of the left auricle. It may be observed in cases without a mitral systolic murmur and may not be present in cases of mitral insufficiency with systolic murmur. The absence of left auricular systolic expansion cannot rule out the existence of mitral insufficiency, since the systolic mitral reflux may be too slight to cause dilatation of the auricle. The degree of left auricular systolic expansion seems to be related to the volume of mitral systolic reflux and increases with the evolution of the mitral valve lesion; its repercussions on the pulmonary circulation are similar to those of tricuspid insufficiency on the liver and systemic circulation.

LUISADA

Dotter, C. T., and Steinberg, I.: Clinical Angiocardiography: A Critical Analysis of the Indications and Findings. Ann. Int. Med. **30:** 1104 (June), 1949.

During the past eleven years, angiocardiographic study of over 1,000 patients has been conducted by the authors without fatality, thus indicating the safety of this diagnostic method. In the presence of certain pathologic states, angiocardiography has emerged as an indispensable diagnostic technic. Contrast cardiovascular visualization has been shown to be of its greatest value in the diagnosis of the following conditions: Coarctation of the aorta; tetralogy of Fallot and related lesions; isolated pulmonic stenosis; anomalous pulmonary veins; aneurysms, congenital and acquired; pericardial effusion; uncomplicated syphilitic aortitis; mediastinal tumors; and bronchogenic carcinoma. The understanding of various other abnormal conditions such as patent ductus arteriosus, septal defects, hypertensive, arteriosclerotic, rheumatic, and pulmonary disease has been enhanced by angiocardiographic study, although diagnosis in such conditions is usually made without resort to contrast visualization. An attempt has been made in this report briefly to summarize the significant angiocardiographic findings in the above clinical conditions, and to suggest the circumstances under which this method of examination is most productive.

WENDKOS

Luisada, A. A., and Fleischner, F. G.: Fluorocardiography (Electrokymography). Am. J. Med. **6:** 756 (June), 1949.

The authors describe the technic of fluorocardiography (electrokymography) as well as observations on normal and abnormal subjects. The method permits the recording on a continuous film of either the motions of the border of the cardiovascular silhouette, as observed on the fluoroscopic screen, or changes in density of the cardiovascular shadow. Typical tracings in normal subjects are presented. Special studies of normal physiology are reported: the velocity of the arterial waves in the pulmonary circulation, the temporal relationship between the contractions of the right and left heart, the isometric relaxation period of the left ventricle, and attempts

at measurement of blood pressure in the lesser circulation.

Observations of clinical conditions include a study of the dynamics of the left auricle and pulmonary veins in mitral valve lesions as well as findings in myocardial infarction. Additional clinical observations include studies in uncomplicated cardiac shunts, in chronic cor pulmonale, in aortic aneurysms and mediastinal tumors, in arteriovenous fistula, in pericarditis with effusion, and in bundle branch block.

SCHWARTZ

Meyer, R. R.: A Method for Measuring Children's Hearts. Radiology **53:** 363 (Sept.), 1949.

The author presents a nomogram for measuring cardiac size in children between the ages of 3 and 16 years. The nomogram was constructed from data obtained in 100 cases in which the divergent distortion factors were calculated individually; from these an average and mean distortion factor was calculated and the formula, $A = L \times S \times 0.68$, was obtained, A being the frontal plane area of the cardiac silhouette, L the long diameter in cm. and S the short diameter in cm.

The cardiac area was also measured independently by a planimeter. The maximum variation between the two methods was less than ± 10 per cent.

ZION

SURGERY AND THE CARDIO-VASCULAR SYSTEM

Parsons, W. H. and Purks, W. K.: The Elderly Patient as a Surgical Risk: An Analysis of Three Hundred and Twenty-Two Operations Performed on Two Hundred and Forty-Four Patients Sixty Years of Age and Over. Arch. Surg. **58:** 888 (June), 1949.

This paper presents an analysis of 322 operations performed on 244 patients over 60 years of age. There were twenty-nine deaths, a patient mortality of 11.4 per cent and a surgical mortality of 9 per cent. There is a sharp difference, in favor of the white race, between the mortality rates in white and Negro subjects. Age itself, anesthesia, technical considerations, and duration of operation are not important factors in mortality. The nature of the lesion and the procedure necessary to correct it, together with the preoperative complications present and the manner in which they are handled, ultimately determine whether the patient shall live or die.

BECK

Gross, R. E., Bill, A. H., Jr., and Peirce, E. C., 2nd: Methods for Preservation and Transplantation of Arterial Grafts. Surg., Gynec. & Obst. **88:** 689 (June), 1949.

A wholly satisfactory solution to the problem of bridging a gap in large arteries or in the aorta would seem to lie in the direction of providing a vascular graft which is viable, which will resemble the normal vessel after implantation, which can withstand intra-arterial pressures, which will not cause thrombosis, and which will not set up serious reaction in the regional tissues. As a preliminary part of this investigation, a study was made of the effects of transplantation of fresh aorta from one dog to another. The method adopted for the preservation of arterial segments consists in the storage of blood vessels at temperatures just above freezing and immersed in a mixture of 10 per cent homologous serum in a balanced salt solution to which are added a buffer, a pH color indicator, and streptomycin and penicillin. Tissue culture studies have shown that viability is maintained for thirty-five to forty days in blood vessels stored in this way. The factor of immunologic reaction between graft and host is exceedingly difficult to evaluate. The series of heterografts was small and no conclusion could be drawn.

On the basis of these laboratory investigations, segments of arteries or aortas secured from human subjects who have died suddenly and without sepsis and stored in the manner described, have subsequently been grafted into 9 human subjects with results which are very promising and which certainly merit further trial and study. A brief summary of each of the 9 cases is presented.

BECK

Cossio, P., and Perianes, I.: Surgical Treatment of the "Cardiac Lung"; Ligation of the Inferior Vena Cava and/or Tricuspid Valvulotomy. J. A. M. A. **140:** 772 (July 2), 1949.

Two surgical procedures are advanced for the treatment of the incapacitating pulmonary congestion resulting from left-sided heart failure which can no longer be managed successfully by medical means. Both procedures, tricuspid valvulotomy and ligation of the inferior vena cava distal to the renal veins, result in a reduction in the right ventricular output and pressure, with resultant diminution of pulmonary congestion and marked symptomatic improvement.

Tricuspid valvulotomy was performed under local anesthesia in 4 patients by means of a specially designed valvulotome introduced into the right jugular vein. One died several hours after operation. The other patients survived and showed definite improvement; 2 of these have survived the procedure by five months and six months, respectively, and the third succumbed to pulmonary infarction two and one-half months after operation. In one additional case the attempt at valvulotomy was abandoned because of sudden collapse while the instrument was in the heart.

Ligation of the inferior vena cava was performed in an unspecified number of cases with an operative mortality in one case and with good results in the rest.

HANNO

Chassin, J. L., and Hinton, J. W.: Hyperpyrexia following Thoracolumbar Sympathectomy. J. A. M. A. **140:** 873 (July 9), 1949.

During a heat wave, 2 patients who had recently undergone extensive bilateral thoracolumbar sympathectomies developed hyperpyrexia. In one patient no sweating was observed, and in the second patient perspiration was limited to one side of the face. The fever in both cases responded to measures designed to reduce the environmental and body temperature (cold wet pack, ice bags, oxygen tent). The authors point out that because of the abolition of most of the sweating mechanism, patients who have recently been subjected to extensive sympathectomies are unusually susceptible to high environmental temperatures.

HANNO

Bland, E. F., and Sweet, R. H.: A Venous Shunt for Advanced Mitral Stenosis. J. A. M. A. **140:** 1259 (Aug. 20), 1949.

In an effort to prevent the repeated bouts of acute pulmonary edema secondary to advanced mitral stenosis, the authors have devised a new surgical procedure which provides an extra-cardiac shunt from the high pressure left auricle and pulmonary vein area into the systemic venous bed. This is effected by anastomosing the dorsal segment branch of the right inferior pulmonary vein to the azygos vein.

Five patients have undergone this procedure. In 3 cases, with postoperative follow-up of from four months to one year, there has been marked improvement; a fourth patient has done well in the two months following surgery; and one patient died eleven days postoperatively of a severe recurrence of acute rheumatic fever.

HANNO

McQuiston, William O.: Anesthetic Problems in Cardiac Surgery in Children. Anesthesiology **10:** 590 (Sept.), 1949.

In his discussion of anesthetic problems in cardiac surgery in children, the author states that the extreme hypoxia of cardiac children makes depression of metabolic activity and psychic sedation the most important considerations of preoperative medication. He recommends the use of relatively large doses of morphine and atropine, or morphine and scopolamine, on all cases. Age, not weight, is the determining factor in the size of the dose.

Before making a choice of anesthetic agent or technic to be used for an operative procedure, one must consider the requirements of both the patient and the surgeon. Cyclopropane has been used as the principal agent for all cardiac surgical procedures carried out by the author. All children are intubated before being turned on their sides. Atropine in solution is used to stimulate heart action. The use of hypothermia to reduce metabolism during operation, particularly in hypoxic children, is suggested.

Operative complications such as pulmonary decompensation are discussed. For the postoperative complication of laryngeal edema, the authors place the children in the "steam room," a room with very high humidity but with a maximum temperature of 75 F. The author reports anoxia as the most frequent cause of death in the series of patients studied. Cerebral hemorrhage or cerebral thrombosis was the next most frequent cause of death.

BELLET

OTHER SUBJECTS

Barbera, G., and Triolo, R.: On the Mechanism of Production of the Venous Hum. Cuore e circolaz. **33:** 1 (Feb.), 1949.

The authors studied the venous hum in 28 patients with anemia by measuring the viscosity of blood, the hematocrit, the rate of blood flow, and the arterial and venous pressure.

The authors conclude that the venous hum is present when the following factors occur: (1) *Mechanical factor*: sudden narrowing of the vessel lumen. (2) *Hemodynamic factor*: changes of blood flow or viscosity. (3) *Pressure factor*: changes of venous pressure.

LUISADA

Courtice, F. C., and Gunton, R. W.: The Determination of Blood Volume by the Carbon Monoxide and Dye (T-1824) Methods in Rabbits. J. Physiol. **108:** 405 (June), 1949.

The authors studied the carbon monoxide method of blood volume determination in rabbits. Simultaneous measurements by carbon monoxide and Evans blue (T-1824) methods show no significant differences. The accuracy of the carbon monoxide method was further tested by repeat determinations and by the addition and removal of known amounts of blood.

Use of a standard closed-circuit breathing system offers certain advantages over the dye method. Only two small blood samples are needed, hemolysis is of no importance, and repeated determinations may be made several times in one day with the same degree of accuracy.

However, rabbits appear to be capable of wide variations in fluid adjustment, in that plasma volume was significantly affected by variations in the fluid content of the diet.

WAIFE

AMERICAN HEART ASSOCIATION, INC.

1775 Broadway, New York 19, N. Y,
Telephone Plaza 7–2045

ANNUAL MEETING IN SAN FRANCISCO, JUNE 22–25

The Annual Meeting and Twenty-third Scientific Sessions of the Association will be held this year at the Fairmont Hotel, San Francisco, June 22–25. Early reservations are advised and arrangements should be made through the A. M. A. Hotel Committee, Convention Bureau, San Francisco.

The first Scientific Session is scheduled for Thursday afternoon, June 22. The annual meeting of the Assembly will be held Saturday afternoon, June 24, and the annual dinner the same evening.

Dr. Louis E. Martin, 1136 West Sixth St., Los Angeles 14, is Chairman of the Program Committee for the Scientific Sessions. All who desire to present papers at the meetings should forward to Dr. Martin an abstract (in triplicate) of the proposed presentation of not more than 300 words. The deadline for the receipt of abstracts is March 1. Dr. Hugh McCulloch, of Chicago, is Chairman of the Program Committee of the American Council on Rheumatic Fever and Dr. Meyer Friedman, of San Francisco, is Chairman of the Program Committee of the Section on the Circulation.

The members of the Program Committee, with Dr. Martin, are:

Graham Asher, M.D., 1220 Professional Bldg., Kansas City, Mo.
Walter Bauer, M.D., Massachusetts General Hospital, Boston, Mass.
Robert H. Bayley, M.D., Oklahoma University, School of Medicine, Oklahoma City, Okla.
Richard J. Bing, M.D., Johns Hopkins Hospital, Baltimore, Md.
Meyer Friedman, M.D., Mount Zion Hospital, 2200 Post Street, San Francisco, Calif.
William Goldring, M.D., 1088 Park Avenue, New York, N. Y.
Robert E. Gross, M.D., Children's Hospital, 330 Longwood Avenue, Boston, Mass.
Hans Hecht, M.D., University of Utah Medical School, Salt Lake City, Utah
William P. Holbrook, M.D., 2430 E. 6th Street, Tucson, Ariz.
Franklin D. Johnston, M.D., P.O. Box 276, Ann Arbor, Mich.
Hugh McCulloch, M.D., La Rabida Sanitarium, Chicago, Ill.
Johnson McGuire, M.D., 2583 Grandin Rd., Cincinnati, Ohio
Edgar M. McPeak, M.D., 4705 Montrose Blvd., Houston, Texas
Ernest W. Page, M.D., University of California, Medical School, San Francisco 22, Calif.
Irvine H. Page, M.D., Cleveland Clinic, Euclid Ave. and 93rd St., Cleveland, Ohio
Helen B. Taussig, M.D., Johns Hopkins Hospital, Medical School, Baltimore, Md.
William Paul Thompson, M.D., 1930 Wilshire Blvd., Los Angeles, Calif.
Harry E. Ungerleider, M.D., 393 Seventh Avenue, New York, N. Y.
Paul D. White, M.D., 264 Beacon Street, Boston, Mass.

NATIONAL CONFERENCE ON CARDIOVASCULAR DISEASES

A National Conference on Cardiovascular Diseases is being held this month (January 18–20) in Washington, D. C. under the joint sponsorship of the Association and the National Heart Institute. Dr. H. M. Marvin, President of the Association, and Dr. C. J. Van Slyke, Director of the National Heart Institute, are the Co-Chairmen. Dr. Paul D. White, a former President of the Association, was Chairman of the steering committee of the Conference.

The Conference is the first national meeting to include representatives of the various medical disciplines and the ancillary professional fields concerned with a cardiovascular program. It is expected to develop a concrete program of action to correlate an all-out national attack on the heart disease problem embracing the resources of all voluntary and official agencies in the field.

INTERNATIONAL CONGRESS IN PARIS NEXT SEPTEMBER

The First International Congress on Cardiology will be held in Paris, France, next Sep-

tember 3–9. Professor Charles Laubry, of Paris, is the General Chairman. Dr. Paul D. White has been named the Association's official delegate, with Dr. H. M. Marvin as deputy. Arrangements for transportation and hotel accommodations may be made through Mr. Gabriel Reiner, Cosmos Travel Bureau, Inc., 40 West 45th St., New York 19, N. Y. or any other travel agency.

Physicians desiring to present a paper at the Paris meetings should send a 250–300 word abstract to Dr. Charles A. R. Connor, Medical Director, American Heart Association, 1775 Broadway, New York 19, N. Y.

DR. MARVIN APPOINTED TO THE NATIONAL HEART ADVISORY COUNCIL

Dr. H. M. Marvin, President of the Association, was recently appointed to a four-year term as member of the National Heart Advisory Council, the chief consultative group for the National Heart Institute of the U. S. Public Health Service.

The National Heart Advisory Council comprises six medical and six lay members, plus four ex-officio members representing the U.S.P.H.S., the Army, Navy and Veterans Administration. Dr. Paul D. White and Dr. Tinsley R. Harrison, former Presidents of the Association, are also members of the Council. Dr. White is, in addition, Executive Director of the Council and Chief Medical Adviser to the Institute.

CASES SOLICITED FOR REGISTRY OF CARDIOVASCULAR PATHOLOGY

Contribution of cases is being currently solicited for the Registry of Cardiovascular Pathology which has been set up, under the Association's sponsorship, in the American Registry of Pathology at the Armed Forces Institute of Pathology in Washington, D. C. Dr. Wallace M. Yater is Chairman of the Registry Committee and its other members are Doctors Jesse E. Edwards, Jane Sands Robb, Joseph T. Roberts, and Helen B. Taussig. Communications regarding the registry should be addressed to The Director, Armed Forces Institute of Pathology, Washington 25, D. C.

The scope of the Registry is outlined as: (1) Congenital anomalies of the heart and larger blood vessels. (2) Subacute bacterial endocarditis. (3) The so-called "diseases of the collagen system," including polyarteritis nodosa, temporal arteritis, disseminated lupus erythematosus, Libman-Sacks endocarditis, scleroderma, and amyloidosis of the heart. (4) Primary tumors of the heart, pericardium, blood vessels and lymphatics, including rhabdomyomatosis and glycogen-storage disease.

Also included are cases illustrating other diseases of the heart and larger blood vessels, in which consultation is desired or which are of especial interest because of rarity or noteworthy clinicopathologic correlation.